Title: A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT)

NCT Number: NCT04329949

Date: 20 January 2020

CLINICAL STUDY PROTOCOL CORT125134-553

Title	A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT)
Investigational Product	Relacorilant (CORT125134)
Medical Monitor	[redacted]
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA +1 (650) 327-3270
Version	Amendment 1
Date	20 January 2020

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Council for Harmonisation Good Clinical Practice guidelines, and with the ethical principles contained in the Declaration of Helsinki (1989), or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human study participants. Compliance with these standards provides assurance that the rights, safety, and well-being of study participants are protected.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

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APPROVAL STATEMENT

The undersigned has reviewed the format and content of the above protocol and approved for issuance.

[redacted]

PROTOCOL SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study Number**
Corcept Therapeutics	Relacorilant (CORT125134)	CORT125134-553

Title of Study

A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT)

Study Centers

Approximately 30 centers in the United States.

Phase of Development

Phase 3

Study Objectives

All study objectives apply to patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with relacorilant in combination with nab-paclitaxel.

Primary

- To evaluate the objective response rate (ORR), defined as the percentage of patients with measurable disease at baseline who achieve confirmed complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, according to blinded independent central review (BICR)

Secondary

Efficacy

- To evaluate the ORR per RECIST v1.1, as assessed by the Investigator
- To evaluate best overall response per RECIST v1.1
- To evaluate the duration of response (DOR), as assessed by the Investigator and BICR
- To evaluate disease control rate (DCR) (CR, PR, or stable disease) at 18 weeks, as assessed by the Investigator
- To evaluate progression-free survival (PFS), as assessed by the Investigator
- To evaluate overall survival (OS)
- To evaluate PFS rate at 3, 6, and 12 months
- To evaluate OS rate at 3, 6, and 12 months
- To assess cancer antigen 19-9 (CA19-9) response at 8 and 16 weeks, in patients who have elevated CA19-9 at baseline
- To assess tumor response based on changes in fluorodeoxyglucose-positron emission tomography (FDG-PET) scan from baseline (screening) to 6 weeks per European Organization for Research and Treatment of Cancer (EORTC) criteria, according to BICR
- To evaluate the time to progression (TTP). The duration of disease control on prior nab-paclitaxel therapy (if applicable) and on the most recent therapy will also be described.

Safety

- To characterize the exposure-toxicity of relacorilant in combination with nab-paclitaxel
- To assess the safety and tolerability of relacorilant in combination with nab-paclitaxel

Pharmacokinetics

- To assess the pharmacokinetics (PK) of relacorilant in combination with nab-paclitaxel

Population

Eligible patients are those with metastatic pancreatic adenocarcinoma (mPDAC) who have received at least 2 prior lines of therapy for pancreatic ductal adenocarcinoma (PDAC) in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy.

Number of Patients Planned

Approximately 80 patients will be enrolled in the study.

Methodology

This is a Phase 3, single-arm, open-label, multicenter study to assess the safety and effectiveness of relacorilant in combination with nab-paclitaxel in patients with mPDAC.

The study consists of the following study periods:

- **Screening Period:** Within 21 days prior to the first dose of relacorilant.
- **Treatment Period:** Both relacorilant and nab-paclitaxel will be administered during the Treatment Period, starting on Cycle 1 Day 1 and continuing until disease progression, unacceptable toxicity, or other treatment discontinuation criteria are met. Relacorilant (starting dose, 100 mg) will be taken once daily and nab-paclitaxel 80 mg/m^2 will be administered on Days 1, 8, and 15 of each 28-day cycle. All patients, with exception of patients with absolute neutrophil count >10,000/mm^3, will receive prophylactic G-CSF to reduce the risk of neutropenia starting 1 day after each nab-paclitaxel infusion. A minimum of 2 doses of G-CSF (filgrastim [5 µg/kg/day]) is recommended.
- **Safety Follow-Up Period:** Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of study treatment. Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments per the Schedule of Assessments (every 6 to 8 weeks) until unequivocal disease progression.
- **Long-Term Survival Follow-Up Period:** All patients will be followed every 3 months after the end of treatment, to document dates of and response to subsequent treatments, and for survival.

Radiographic tumor assessments will be conducted using computed tomography (CT) with contrast of the chest, abdomen, and pelvis using standard multiphasic (pancreas) CT imaging protocol guidelines. Magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis is acceptable, with Medical Monitor approval, if CT with contrast cannot be done. The same method should be used for each assessment for a particular patient. Prior to initiating therapy, a baseline tumor scan is required within 21 days prior to the first dose of relacorilant. Subsequent CT/MRI scans will be obtained every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days). CT/MRI scans will continue per this schedule until unequivocal disease progression is documented, including in patients who prematurely discontinue therapy. Tumor response will be assessed by BICR, and by the Investigator, using RECIST v1.1. CR and PR will be confirmed with a subsequent scan at least 4 weeks from the first response.

The same images (CT or MRI) acquired for radiographic tumor assessments will undergo additional imaging assessments for changes in skeletal muscle mass to determine the presence of sarcopenia.

A baseline FDG-PET scan will be obtained prior to initiating therapy and a post-baseline FDG-PET scan will be obtained 6 weeks (±7 days) from Cycle 1 Day 1.

Pharmacodynamics/Biomarkers

Patients will be requested to provide an archival or recent tumor biopsy, if available, for exploratory markers relevant to pancreatic cancer or the mechanism of action. Patients will also have the option to consent to provide an additional on-study biopsy obtained during a procedure conducted as part of their standard of care. Pharmacodynamic markers will include mRNA gene panel (blood and tumor expression profiles), cytokines, and other exploratory biomarkers.

Pharmacokinetics

PK will be characterized after dosing with the combination of nab-paclitaxel and relacorilant, on Cycle 1 Days 1, 2, and 15. Blood samples will be collected for determination of plasma PK parameters of relacorilant and/or its metabolites (CORT125336; CORT125337; CORT125295). Blood samples will be also be collected for determination of plasma PK parameters of nab-paclitaxel.

Patient-Reported Outcomes and Quality of Life

Baseline patient-reported outcomes (PRO) and quality-of-life (QoL) assessments must be collected prior to the first dose of relacorilant. Post-baseline assessments will be collected at the beginning of every cycle starting at Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-day Post-Treatment Follow-Up Visit.

Duration of Treatment and Duration of Study

Patients will receive treatment until reaching unequivocal progressive disease (PD) (per RECIST v1.1) as determined by the Investigator, experiencing unmanageable toxicity, or until other treatment discontinuation criteria are met. All patients will be followed for documentation of disease progression and survival information (i.e., date and cause of death) and subsequent treatment information (i.e., date/duration of treatment, response, and subsequent PD). Survival follow-up will continue every 3 months until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to conduct periodic and ad hoc medical and/or statistical reviews of available safety data to protect the safety and ethical interest of patients and protect the scientific validity of the study. The IDMC will also perform an interim assessment of efficacy data after 40 patients have enrolled and completed at least 12 weeks of treatment, including the second radiographic tumor assessment, and have at least 1 post-baseline tumor assessment with a result other than nonevaluable, or discontinued the study due to disease progression or toxicity. Enrollment will be paused such that the interim efficacy assessment can be conducted by the IDMC before additional patients are enrolled.

Key Criteria for Inclusion

Key Inclusion Criteria

Each patient must meet the following criteria to be eligible for enrollment into this study:

1. Have histologically confirmed PDAC with metastatic disease.
2. Have received at least 2 prior lines of therapy for PDAC in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy.
3. Have received no more than 4 prior lines of cytotoxic or myelosuppressive therapy for PDAC.
4. Have a measurable lesion at baseline (within 21 days prior to the first dose of relacorilant) per RECIST v1.1, as assessed by the Investigator.

   Note: Standard multiphasic (pancreas) protocols should be used for all radiographic tumor assessments. The exact same image acquisition and processing parameters should be used throughout the study.
5. Willingness to provide blood samples and tumor tissue (primary or metastatic) for research purposes.
6. Available assessments of CA19-9 (or carcinoembryonic antigen [CEA] and cancer antigen 125 [CA-125] in non-CA19-9 elevated tumors) within 14 days prior to first dose of relacorilant.
7. Karnofsky performance status (KPS) score of ≥70. Two observers are required to assess KPS. If discrepant, the one with the lowest assessment will be considered true.
8. Any significant or symptomatic amounts of ascites have been drained prior to enrollment.

9. Have adequate gastrointestinal absorption. If the patient has undergone gastric bypass surgery and/or surgery of gastrointestinal or hepatobiliary tract, the patient must demonstrate adequate absorption as evidenced by albumin ≥3.0 g/dL, controlled pancreatic insufficiency (if present), and lack of evidence of malabsorption.
10. Have adequate organ and marrow function meeting the following criteria:
    a. Absolute neutrophil count ≥1,500 cells/mm^3
    b. Platelet count ≥100,000/mm^3
    c. Hemoglobin ≥9 g/dL
    d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) (or ≤4 × ULN in patients with liver metastases)
    e. Total bilirubin ≤1.5 × ULN
    f. Creatinine clearance (measured or estimated) >45 mL/min/1.73m^2
    g. Albumin ≥3 g/dL (≥30 g/L)

Key Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Have pancreatic neuroendocrine tumors, lymphoma of the pancreas, acinar pancreatic cancer, or ampullary cancer.
2. Have known untreated parenchymal brain metastasis or have uncontrolled central nervous system metastases. Patients with treated and controlled brain metastases must not require steroids and must be neurologically stable without corticosteroids for a minimum of 3 weeks prior to Cycle 1 Day 1 to be eligible.
3. Have a clinically relevant toxicity from prior systemic cytotoxic therapies or radiotherapy that in the opinion of the Investigator has not resolved to Grade 1 or less prior to enrollment, including peripheral neuropathy that is ongoing and greater than Grade 1 in severity, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.
4. Have taken the following medications prior to enrollment:
    a. An investigational product, cytotoxic chemotherapy or targeted agent within 14 days.
    b. Radiotherapy within 21 days.
    c. Palliative radiotherapy within 1 week of Cycle 1 Day 1, or if toxicities from radiotherapy are Grade 2 or higher in severity or have not returned to baseline. If palliative radiation therapy included the pelvis, a minimum of 3 weeks is required between palliative radiotherapy and the first dose of study treatment.
    d. Systemic or prescription strength topical corticosteroids for the purposes of treating a chronic nononcologic indication within 21 days.
5. Have a requirement for treatment with chronic or frequently used oral or inhaled corticosteroids for medical conditions or illnesses (e.g., rheumatoid arthritis, asthma, or immunosuppression after organ transplantation).
6. Have had any major surgery within 21 days prior to enrollment.
7. Have had endoscopic retrograde cholangiopancreatography with persistence of any of the following:
    a. Bilirubin ≥1.5 × ULN
    b. Amylase >2 × ULN and abdominal pain or amylase >3 × ULN (with or without symptoms)
    c. Fever or signs of infection
    d. Decreasing hemoglobin or signs of blood loss
8. Have a rapid decline in KPS or serum albumin (≥20%), or have progressive pain symptoms indicative of rapid clinical deterioration in the opinion of the Investigator, prior to enrollment. These patients will become ineligible if rapid decline is observed during the Screening Period.

Study Treatment, Dose, and Mode of Administration

Study treatment consists of the investigational product, relacorilant, in combination with nab-paclitaxel.

Investigational product (Relacorilant): 100-mg or 25-mg softgel capsules.

Relacorilant 100 mg is to be administered orally once daily in the morning, each day. After the first cycle, patients who tolerate their current dose of relacorilant will have their relacorilant dose increased in 25-mg increments to a maximum dose of 150 mg once daily.

Patients should be encouraged to take relacorilant with food and room temperature water.

Nab-paclitaxel (Abraxane®): Nab-paclitaxel 80 mg/m^2 is to be administered via intravenous infusion over 30 minutes (±5 minutes) on Days 1, 8, and 15 of each 28-day cycle.

Reference Product, Dose, and Mode of Administration

Not applicable.

Key Criteria for Evaluation

Primary Endpoint

Efficacy

- ORR, defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR

Secondary Endpoints

Efficacy

- ORR per RECIST v1.1, according to Investigator assessment
- Best overall response, defined as the best response recorded from the date of enrollment across all time points during study observation period, per RECIST v1.1 according to BICR
- Best overall response per RECIST v1.1 according to Investigator assessment
- DOR as measured from the date that the criteria are met for CR or PR until the first date that PD is objectively documented and determined by the Investigator
- DOR as measured from the date that the criteria are met for CR and PR until the first date that PD is objectively documented and determined by BICR
- DCR, defined as the percentage of patients who have achieved CR, PR, or stable disease for ≥18 weeks, as determined by the Investigator
- PFS, defined as the time from the date of enrollment to the date the patient experiences unequivocal disease progression per RECIST v1.1, as determined by the Investigator, or death (all causes of mortality)
- OS, defined as the time from enrollment until the date of death from any cause
- PFS rate (proportion of patients who have not progressed) at 3, 6, and 12 months
- OS rate (proportion of patients surviving) at 3, 6, and 12 months
- Change in CA19-9 from baseline at 8 weeks and 16 weeks in patients who have elevated CA19-9 (CA19-9 >ULN) at baseline
- CA19-9 response, at 8 weeks and 16 weeks, defined as the percentage of patients with elevated CA19-9 at baseline who have ≥50% reduction in CA19-9
- Tumor response assessed by FDG-PET at 6 weeks per EORTC criteria, according to BICR
- TTP on study treatment, as determined by the Investigator

Safety

- Study drug exposure
- Exposure-toxicity and exposure-response of relacorilant and nab-paclitaxel

- Adverse events (AEs) (including frequency, severity, and relationship to study treatment) and deaths
- Change from baseline in clinical laboratory tests
- Change from baseline in vital signs (including blood pressure, heart rate)
- Interpretation of electrocardiogram assessments (normal, abnormal clinically insignificant, or abnormal clinically significant)
- Physical examination findings

Pharmacokinetics

- Primary PK parameters of relacorilant and nab-paclitaxel estimated from PK sampling on Cycle 1 Days 1, 2, and 15

Statistical Methods

Analysis Populations

- Intent-to-Treat (ITT) Population/Safety Analysis Population: All patients enrolled and treated with at least 1 dose of study treatment
- Evaluable Population: All patients in the ITT Population who have at least one post-baseline radiographic tumor assessment available (with results other than nonevaluable)
- PK Population: All enrolled patients who have PK data collected and available for analysis

Statistical Analyses

Analyses of safety and efficacy will focus on estimation of treatment effects via descriptive statistics and confidence intervals (CIs). Baseline will be defined as the most recent value prior to the first dose of relacorilant.

Efficacy Analyses

Response rate endpoints will be summarized by providing the point and interval estimates. Time-to-event variables will be summarized using Kaplan-Meier estimates and plots. Event probabilities at 4-, 6-, and 12-month time points and the median time-to-event (if estimable) will be presented.

The primary analysis of ORR according to BICR will be performed in the ITT Population. ORR will also be analyzed in the Evaluable Population. The point estimate and 95% CI will be provided using the Clopper-Pearson method. Patients in the ITT Population with no valid post-baseline radiographic tumor assessments will be considered nonresponders.

Secondary endpoints will also be analyzed in the ITT and Evaluable Populations.

Safety Analyses

The incidence of treatment-emergent adverse events (TEAEs), defined as AEs occurring after the first dose of study treatment through 30 days after the final dose of study treatment, will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. TEAEs will be further summarized by severity and relationship to study treatment.

Tabular summaries will be created for TEAEs, TEAEs leading to discontinuation of study treatment (i.e., relacorilant or nab-paclitaxel), TEAEs leading to dose reduction or interruption, Grade ≥3 TEAEs, and serious AEs. A by-patient listing of AEs will also be created.

All deaths and causes of deaths will be summarized and listed.

Pharmacokinetic Analyses

PK parameters of nab-paclitaxel and relacorilant and its metabolites will be calculated, and analyte concentration versus time plots will be provided. PK analyses will be performed on the PK Population.

Pharmacodynamic Analyses

Pharmacodynamic parameters and biomarker results will be listed and summarized using descriptive statistics, as appropriate.

Patient-Reported Outcomes and Quality of Life

Data collected using the PRO instruments and QoL assessments will be listed and summarized using descriptive statistics.

Sample Size

In this single-arm, estimation study, the efficacy analysis will include the calculation of a 95% CI around the ORR point estimate in the ITT Population. The lower bound of the 95% CI for ORR will be evaluated to exclude <5%. In addition to evaluating the point and interval estimate around the ORR, the efficacy in this study will be evaluated by examining the DOR, as well the DCR, of at least 18 weeks. A total of 80 patients in the ITT Population are expected in this study to provide sufficient precision for the interval estimates for the ORR.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BICR	blinded independent central review
CA-125	cancer antigen 125
CA19-9	cancer antigen 19-9
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
COX2	cyclooxygenase 2
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
DLT	dose-limiting toxicity
DUSP1	dual-specificity phosphatase 1
ECG	electrocardiogram
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose-positron emission tomography
FOLFIRINOX	folinic acid, fluorouracil, irinotecan, and oxaliplatin
FOLFOX	folinic acid, fluorouracil, and oxaliplatin
GC	glucocorticoid
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GR	glucocorticoid receptor

Abbreviation	Definition
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
K_i	inhibition constant
KPS	Karnofsky performance status
MedDRA	Medical Dictionary for Regulatory Activities
mPDAC	metastatic pancreatic ductal adenocarcinoma
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
QC	quality control
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
RSI	reference safety information
SAE	serious AEs
SAP	statistical analysis plan
SD	standard deviation
SoA	Schedule of Assessments
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	standardized uptake value
TEAE	treatment-emergent AEs
TTP	time to progression
ULN	upper limit of normal
US	United States
WHO	World Health Organisation

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Relacorilant (also referred to as CORT125134) is a small molecule competitive antagonist of the glucocorticoid receptor (GR) being developed by Corcept Therapeutics (Corcept) for indications that may benefit from the modulation and/or antagonism of GR. In preclinical tumor models, GR has been demonstrated to be involved in chemotherapy resistance, with stimulation of GR shown to reduce chemotherapy sensitivity and blockade of GR shown to enhance chemotherapy sensitivity (Skor et al. 2013, Isikbay et al. 2014). Thus, as a selective and potent GR antagonist, relacorilant has the potential to provide a clinical benefit in oncologic indications in combination with appropriate chemotherapeutic agents by reversing the GR-mediated chemotherapy resistance mechanism and potentially restoring tumor sensitivity to the chemotherapeutic agent.

This Phase 3 study (**REL**acorilant **I**n Pancreatic **A**denocarcinoma with **N**ab-Pacli**T**axel [RELIANT]) is designed to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics, of relacorilant in combination with nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). Patients must have histologically confirmed pancreatic ductal adenocarcinoma (PDAC) to participate.

1.1 Pancreatic Cancer

Pancreatic cancer is the third leading cause of cancer-related death in the United States and is characterized as a highly lethal form of cancer. Approximately 56,770 people are expected to be diagnosed with pancreatic cancer in the United States (US) and more than 45,750 are expected to die from the disease in 2019 (ACS 2019). Worldwide, pancreatic cancer is the seventh leading cause of cancer death in both males and females; there were approximately 459,000 new cases of pancreatic cancer in 2018 and approximately 432,000 deaths due to the disease (Bray et al. 2018).

Typically, patients present with a later stage of cancer when a surgical cure is no longer an option. The 5-year relative survival rate for patients with pancreatic cancer is 8.5%, and among patients with metastatic disease the 5-year survival rate is only 2.7% (ACS 2019). Pancreatic cancer is one of the few tumor types for which survival has not improved substantially in more than 40 years (ACS 2019), demonstrating a critical unmet medical need in this area. Over the past decade, first-line treatment for mPDAC has shifted from gemcitabine monotherapy toward combination therapy with folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine combined with nab-paclitaxel. A large proportion of patients (56%) with mPDAC proceed to receive second-line chemotherapy with a wider spread of regimens used consisting of either FOLFOX (folinic acid, fluorouracil, and oxaliplatin), gemcitabine monotherapy, gemcitabine + nab-paclitaxel, FOLFIRINOX, or capecitabine (Abrams et al. 2017). Once first- and second-line treatments are exhausted for patients with advanced pancreatic cancer, options are limited and patients often move to palliation and pain control. The median overall survival (OS) for second-line therapies range from 3.3 to 8.8 months (Portal et al. 2015), with only 22% of patients with metastatic pancreatic cancer receiving third-line chemotherapy (Abrams et al. 2017).

Study CORT125134-553 is the first study designed to evaluate the efficacy of relacorilant and nab-paclitaxel in patients with third-line or greater PDAC with metastatic disease. The primary

efficacy endpoint is objective response rate (ORR). Historical data in studies of third-line therapies for mPDAC are limited but suggest an ORR approaching 0% (Wang-Gillam et al. 2019, Le et al. 2019, Macarulla et al. 2017). Similarly, a retrospective review carried out in patients with pancreatic adenocarcinoma who received nab-paclitaxel monotherapy after experiencing disease progression on standard treatments yielded an ORR of 0% (0 out of 17 patients achieved a complete response [CR] or partial response [PR]) (Peddi et al. 2013). Another study evaluated nab-paclitaxel in patients who received a gemcitabine-based regimen (inclusive of patients on second-line therapy); in this study, an ORR of 5% was observed (1 PR was reported out of 19 patients treated) (Hosein et al. 2013). In the current study, based on the low historical ORRs observed in patients with mPDAC treated with a third-line therapy, the lower bound of the 95% confidence interval (CI) for ORR will be evaluated to exclude 10% (Section 9.4).

1.1.1 Therapeutic Hypothesis

The role of GR in chemotherapy resistance in pancreatic cancer is of interest. Evaluation and staining for GR in 16 samples of pancreatic cancer from a tumor bank demonstrated a mean H score of 131 with a range of 30 to 280 using a validated immunohistochemistry (IHC) assay for GR (Block et al. 2017), demonstrating a significant GR expression in the tumor samples studied.

High rates of GR expression have been shown in several solid tumor types including pancreatic, ovarian, and triple-negative breast cancer (Block et al. 2017) and there is evidence that dysregulation of cortisol may have implications for disease progression (Weinrib et al. 2010). Excess tumor expression of GR could contribute to chemotherapy resistance. In preclinical models, stimulation of GR has been shown to reduce chemotherapy sensitivity and blockade of GR has been shown to enhance chemotherapy sensitivity (Skor et al. 2013, Isikbay et al. 2014). As a selective and potent GR antagonist, relacorilant has the potential to provide a clinical benefit in oncologic indications in combination with appropriate chemotherapeutic agents by reversing GR-mediated chemotherapy resistance and potentially restoring tumor sensitivity to the chemotherapeutic agent. A Phase 1/2 study evaluating the combination of relacorilant and nab-paclitaxel in patients with solid tumors is ongoing (CORT125134-550). This is the first study designed to evaluate the efficacy of relacorilant and nab-paclitaxel in patients with mPDAC after 2 or more prior lines of therapy.

Taken together, the nonclinical and clinical data indicate that GR antagonism may play a role in enhancing or restoring chemotherapy sensitivity in the treatment of patients with pancreatic cancer. The data therefore support the planned evaluation of the combination of relacorilant and nab-paclitaxel in this indication.

1.2 Relacorilant

This section briefly summarizes nonclinical and clinical information on relacorilant. Further details are provided in the relacorilant Investigator's Brochure (IB).

1.2.1 Nonclinical Summary

Nonclinical studies have demonstrated that stimulation with a GR agonist triggers tumor cells to promote the expression of cell survival (anti-apoptotic) genes, enhancing their ability to escape

chemotherapy that would otherwise induce cell death via apoptosis. This mechanism of chemotherapy resistance has been demonstrated with the GR agonist dexamethasone and is reproducible across several tumor cell line models (Zhang et al. 2006, Stringer-Reasor et al. 2015). Furthermore, several in vitro xenograft studies have shown that the addition of GR antagonists to a tumor cell line treated with chemotherapeutic agents, including taxanes, enhances the effects of chemotherapy.

1.2.1.1 In Vitro Pharmacology

Functional GR antagonism was demonstrated in vitro by the ability of relacorilant to block the effects of dexamethasone (a potent GR agonist) on tyrosine aminotransferase activity in human liver-carcinoma (HepG2) and rat hepatoma cell lines (inhibition constants [K_i] 7.2 nM and 1.2 nM, respectively) and in primary hepatocytes from rats, monkeys, mini pigs, and humans. In the human HepG2 tyrosine aminotransferase (TAT) assay, the metabolite, CORT125201, has similar activity to relacorilant. The metabolite, CORT125295, has some activity. CORT125336 and CORT125337 (previously referred to as CORT125134-M2 and CORT125134-M4, respectively) exhibit modest potency.

Relacorilant has high selectivity for the GR, but no significant affinity for the estrogen receptor or the androgen receptor, showing 100%, −1%, and 6% inhibition, respectively, in radioligand binding assays at a 1 μM concentration. In contrast to the GR antagonist mifepristone, relacorilant has considerably greater selectivity for GR over the progesterone receptor, producing only 7% displacement of labeled promegestone at a concentration of 1 μM (relacorilant K_i >10 μM, mifepristone K_i = 1.2 nM) in a progesterone receptor ligand binding assay (Cerep Report 100011862). The selectivity of relacorilant for GR compared with the mineralocorticoid receptor was determined in protein-protein interaction assays. In the GR assay, relacorilant had a K_i of 15 nM, whereas in the analogous mineralocorticoid receptor assay, relacorilant showed no activity at a concentration of 10 μM. A metabolite of relacorilant, CORT125295, is also a selective GR antagonist with no significant affinity for the progesterone or androgen receptor (Cerep Report 100043245).

In safety pharmacology assessments, no remarkable central nervous or respiratory effects were seen in rats or cardiovascular system effects in monkeys at the highest oral dose tested (200 mg/kg relacorilant). In radioligand binding assays, a 1 μM concentration of relacorilant did not produce significant (<50%) inhibition of radioligand binding at 77 of 78 receptors and channels in a panel that included the alpha- and beta-adrenergic, cannabinoid, dopaminergic, gamma-aminobutyric acid, histamine, endothelin, melatonin, leukotriene, cholinergic, opioid, and serotonergic receptors, as well as the transporters for norepinephrine, dopamine, and serotonin. A 1 μM concentration of relacorilant produced 58% inhibition at the cholecystokinin 1 receptor (Cerep Report 100011862). The metabolite CORT125295 has also been tested against a diverse panel of receptors, enzymes and channels and no issues were noted (Cerep Report 100032245).

1.2.1.2 In Vivo Studies

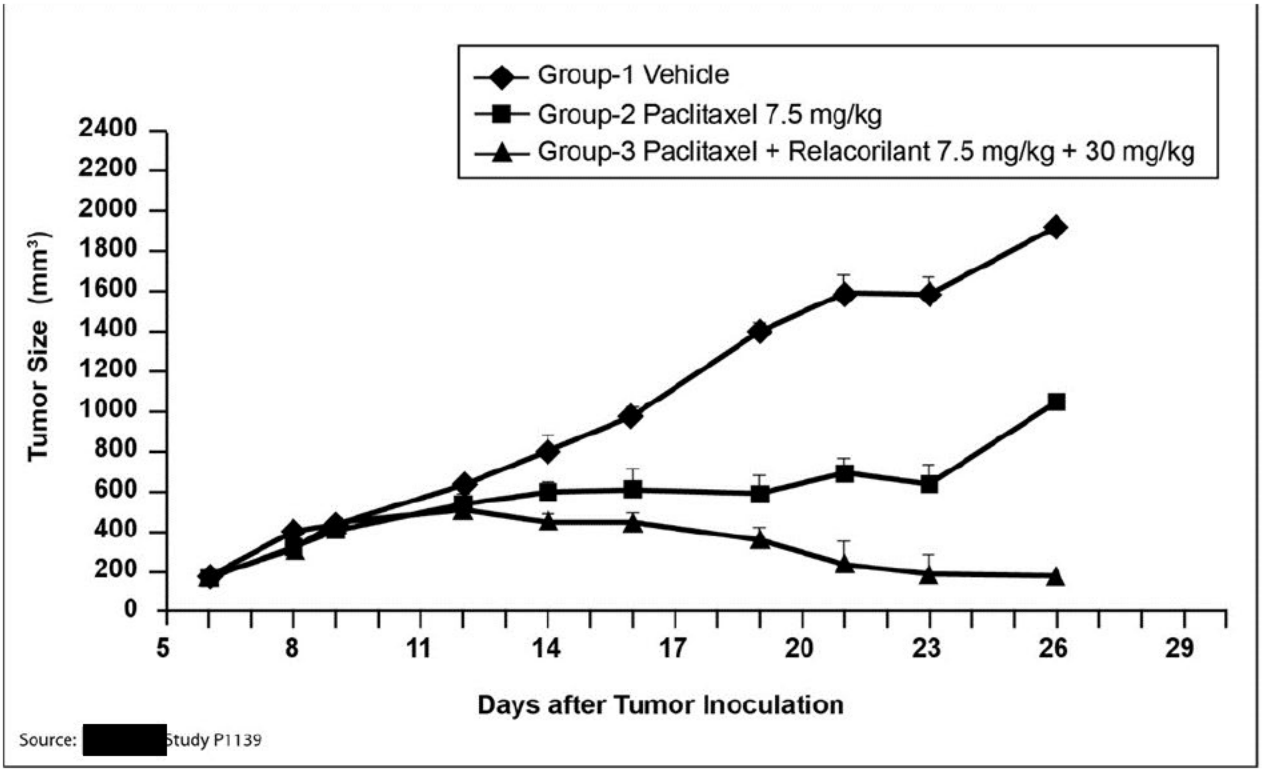
In a rat model of cortisone-induced insulin resistance, relacorilant reduced glucose and insulin levels when administered orally at doses of 30 mg/kg and 7.5 mg/kg twice daily. Relacorilant in

combination with paclitaxel was more effective than paclitaxel alone in a series of mouse cancer xenograft studies, including pancreatic cancer, triple-negative breast cancer, and cervical cancer.

In a xenograft model of pancreatic cancer ([redacted] Study P1139), the efficacy of paclitaxel in combination with relacorilant was assessed in female BALB/c nude mice injected with MIA PaCa-2 cells subcutaneously into the right flank. On Day 6, the mice were administered vehicle, paclitaxel, or paclitaxel in combination with relacorilant. Paclitaxel was administered every 4 days. Relacorilant was administered by oral gavage the day before the chemotherapy, and the same day as the chemotherapy.

As shown in Figure 1, after an initial response to paclitaxel, tumor cells continued to grow despite administration of chemotherapy. In contrast, the combination of relacorilant and paclitaxel provided a statistically significant reduction in tumor growth when compared with paclitaxel alone ($p<0.001$). The reversal of tumor growth demonstrated in the arm treated with relacorilant in combination with paclitaxel suggests that GR antagonism in this model improved the efficacy of paclitaxel.

Figure 1 Effect of Relacorilant in Combination with Paclitaxel in a Pancreatic Cancer Xenograft Model (MIAPaCa-2 Model)



Source: [redacted] Study P1139

1.2.2 Clinical Summary

There are 2 ongoing studies of relacorilant in combination with nab-paclitaxel: one Phase 1/2 study (Study CORT125134-550) in patients with solid tumors, and one Phase 2 study (Study CORT125134-552) in patients with ovarian, fallopian tube, or primary peritoneal cancer.

Available efficacy and safety data from Study CORT125134-550 are briefly summarized below. While preliminary safety data from Study CORT125134-552 are provided, to date, no efficacy analyses have been performed for Study CORT125134-552.

1.2.2.1 Efficacy

Patients in Study CORT125134-550 have been treated with relacorilant doses of 100 mg to 150 mg with a continuous regimen and 150 mg to 200 mg with an intermittent regimen. All treatment regimens included relacorilant in combination with nab-paclitaxel (60 mg/m^2 to 100 mg/m^2).

Preliminary efficacy results were reported in Munster et al. 2019. Data summarized in this section are reflective of the efficacy data from this ongoing study as of the data cutoff (01 June 2019) date. Final efficacy analyses will be performed when the study is complete.

Of the 25 patients with PDAC who were evaluable for response, 3 patients had a PR (2 confirmed, 1 unconfirmed) and 10 patients had stable disease. Disease control (stable disease or better) of 16 weeks or more was observed in 7 patients (28% disease control rate [DCR]). Of the 13 patients with ovarian, primary peritoneal, or fallopian tube cancer who were evaluable for response, 1 patient had confirmed CR, 2 patients had a PR (1 confirmed, 1 unconfirmed), and 6 patients had stable disease. Disease control of 16 weeks or more was observed in 5 patients (38% disease control rate). In addition, confirmed responses were observed in the following tumor types: human papillomavirus-positive vulvar squamous cell cancer (n=1); cholangiocarcinoma, (n=1); and acinar pancreatic cancer (n=1).

In both populations (PDAC and ovarian, primary peritoneal, or fallopian tube cancer), time to progression (TTP) was often several-fold longer than previously achieved on taxane therapy and GR-specific pharmacodynamic responses were observed, underscoring the contribution of relacorilant to disease control. This data is promising and supports further exploration of this regimen in patients with PDAC with metastatic disease.

Study CORT125134-552 is ongoing and no efficacy results are currently available.

1.2.2.2 Safety

Details of all completed and ongoing clinical studies are provided in the IB.

As of the data cutoff date (01 June 2019), 69 patients with late-stage cancer have received at least 1 dose of relacorilant in Study CORT125134-550. Overall, across all dosing regimens studied (Section 1.2.2.1), the most common treatment-emergent adverse events (TEAEs) were fatigue (52.2%), nausea (46.4%), vomiting (44.9%), and diarrhea (42.0%), and the most frequent TEAEs leading to drug interruption were neutropenia (14.5%), vomiting and fatigue (10.1% each). The most common TEAEs considered related to relacorilant occurring in 10% or more of the patients were nausea (26.1%), rash and vomiting (24.6% each), fatigue (23.2%) diarrhea (21.7%), skin hyperpigmentation (18.8%), neutropenia (14.5%), neuropathy peripheral (14.5%), nail disorder (13%), and decreased appetite (11.6%). The most common AE of Grade 3 or higher considered related to relacorilant occurring in 10% or more of patients in any treatment group was neutropenia (11.6%). In the current study, the risk of neutropenia will be managed with

mandatory prophylactic growth factors, monitoring, and nab-paclitaxel dose reduction. Patients will receive G-CSF starting 1 day after each nab-paclitaxel infusion (Section 5.3).

Thirteen patients experienced 1 or more adverse events (AEs) that led to discontinuation of study treatment. Fatigue and thrombocytopenia were the most common AEs (reported in 2 patients each) that led to discontinuation from study treatment. Thirty-three patients who have received at least 1 dose of relacorilant have experienced serious AEs (SAEs). The most common SAEs (occurring in 2% or more of patients) included vomiting (5.8%), atrial fibrillation, abdominal pain, pulmonary embolism, and disease progression (4.3% each), pleural effusion, respiratory failure, febrile neutropenia, neutropenia, pyrexia, colitis, pneumonia, and malignant pleural effusion (2.9% each). Overall, 6 of the 69 patients had TEAEs that led to death. Five of the 6 patients who died succumbed to their underlying cancer as a result of disease progression, intestinal blockage, or respiratory failure, and the Investigator considered the deaths to be unrelated to the study treatment regimen. One patient, who experienced an SAE of Grade 4 neutropenia, developed urosepsis and died; in this case, the Investigator assessed the urosepsis as the cause of death and both events as possibly related to the combination of relacorilant and nab-paclitaxel.

As of 28 August 2019, a total of 6 patients have received study treatment (4 patients with relacorilant in combination with nab-paclitaxel; 2 patients with nab-paclitaxel alone) in the ongoing Study CORT125134-552 in patients with platinum-resistant or platinum-refractory ovarian, primary peritoneal, or fallopian tube cancer. One patient receiving the intermittent relacorilant regimen Grade 3 SAEs (acute kidney injury, anemia and abdominal pain) that resulted in dose interruption; the outcome of all events was considered recovered/resolved. The patient subsequently reported a Grade 3 SAE of wound infection that resulted in discontinuation of study treatment. The patient was enrolled in hospice with subsequent death due to PD; the events were considered unrelated to relacorilant or nab-paclitaxel by the Investigator and Sponsor. Refer to the current version of the relacorilant IB for the safety data for this ongoing study.

1.3 Nab-Paclitaxel

Nab-paclitaxel (Abraxane®) is paclitaxel formulated as albumin-bound nanoparticles. Paclitaxel is a microtubule inhibitor that stabilizes microtubules by preventing depolymerization, which results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. As a result, cells become blocked in the G2/M phase of the cell cycle, which disrupts the mitotic spindles and causes cell death due to prolonged mitotic blockage (Horwitz 1994).

Nab-paclitaxel is indicated for the treatment of metastatic adenocarcinoma of the pancreas as first-line treatment in combination with gemcitabine, and is also indicated for metastatic breast cancer and non-small cell lung cancer (Abraxane USPI 2018; Abraxane SPC 2019).

The most common adverse reactions (in at least 20% of patients) associated with nab-paclitaxel in pancreatic adenocarcinoma are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration.

Warnings and precautions include bone marrow suppression (primarily neutropenia), sensory neuropathy, sepsis, pneumonitis, hypersensitivity, use in patients with hepatic impairment, and

use in pregnancy. The prescribing information indicates that nab-paclitaxel should not be used in patients who have baseline neutrophil counts of <1,500 cells/mm^3 and that patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be rechallenged with the drug. The metabolism of paclitaxel is catalyzed by cytochrome P450 (CYP)2C8 and CYP3A4. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4 (Abraxane USPI 2018).

1.4 Rationale for Study Design and Dose Regimen

This is a Phase 3 open-label single-arm study to evaluate the efficacy, safety, PK, pharmacodynamics, and patient-reported outcomes (PRO) and quality of life (QoL) of relacorilant in combination with nab-paclitaxel in patients with mPDAC. Patients who have received at least 2 prior lines of therapy for PDAC in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy, and have metastatic disease are eligible for the study.

1.4.1 Differences Statement

This is the first study designed to evaluate the efficacy of relacorilant in combination with nab-paclitaxel in patients with mPDAC after 2 or more prior lines of therapy.

1.4.2 Rationale for Study Design

Some solid tumors develop chemotherapy resistance in part via stimulation or upregulation of the GR with subsequent expression of cell survival gene products. Nonclinical and clinical data obtained to date (Section 1.2) support the investigation of relacorilant, a selective and potent GR antagonist, with nab-paclitaxel in patients with mPDAC.

The current standard of care for patients with pancreatic cancer for patients with good performance status includes 2 lines of treatment, with recommended options including a gemcitabine-based regimen (monotherapy or gemcitabine combined with nab-paclitaxel) and a fluoropyrimidine-based regimen. Once first- and second-line treatments are exhausted for patients with advanced pancreatic cancer, treatment options in the third-line setting are limited and patients often move to palliation and pain control. Thus for patients with third-line or greater mPDAC, current guidelines recommend best supportive care or referral to a clinical trial (Tempero et al. 2017), such as this study.

Given the lack of therapeutic options in this refractory patient population, the single-arm open-label design of this study is considered appropriate.

To reduce bias, all radiological images will be centrally reviewed by blinded independent central review (BICR). The primary efficacy endpoint, ORR, will be based on BICR interpretation of the tumor scans per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The ORR obtained with relacorilant + nab-paclitaxel will be interpreted within the context of available data for historical clinical activity of nab-paclitaxel alone.

An interim assessment by an Independent Data Monitoring Committee (IDMC) will be performed after 40 patients have met the specified outcomes (Section 9.5.9). This interim assessment may also inform a protocol amendment to increase the sample size and/or adapt the

study design, if needed, based upon the magnitude and duration of treatment effects, to further support the development of this treatment combination in patients with mPDAC.

1.4.3 Rationale for Dose Selection

The doses of relacorilant 100 mg and nab-paclitaxel 80 mg/m^2 have been used in patients with pancreatic adenocarcinoma in Study CORT125134-550. Preliminary efficacy data from Study CORT125134-550 evaluating nab-paclitaxel in conjunction with relacorilant in patients with pancreatic adenocarcinoma support a clinical benefit in this patient population. (Section 1.2.2.1).

Nab-paclitaxel was selected for combination with relacorilant for the following reasons:

1. Additional anticancer effect by relacorilant has been reproducibly demonstrated in several preclinical models across several tumor cells lines in combination with standard chemotherapeutics, including paclitaxel. Tumor response has also been observed in patients receiving relacorilant in combination with nab-paclitaxel in the Phase 1 Study CORT125134-550, including in patients who have previously received taxane treatment. This supports the proposed mechanism that GR antagonism will delay or reverse chemotherapy resistance.
2. Taxanes are a widely used and efficacious chemotherapy, with applicability to many tumor types.
3. Nab-paclitaxel has a similar safety and efficacy profile to paclitaxel; however, it does not require pretreatment with steroids to avoid allergic reaction and hence is an ideal candidate to evaluate further in the model of GR antagonism to reduce chemotherapy resistance.

1.4.4 Rationale for Dose Regimen

Relacorilant in combination with nab-paclitaxel has been administered using continuous and intermittent dosing regimens to patients with advanced solid tumors in Study CORT125134-550 and has been well tolerated. In the current study, relacorilant will be administered at 100 mg once daily (continuous dosing), with possible increase to a maximum dose of 150 mg once daily (Section 5.1.1), based on preliminary efficacy and safety results observed in Study CORT125134-550.

The initial starting dose of nab-paclitaxel in Study CORT125134-550 was 80 mg/m^2 when dosed with continuous relacorilant (100 mg) to account for the expected CYP3A-mediated drug-drug interaction resulting in increased nab-paclitaxel exposure. Overall, the toxicities observed with the dosing regimen were largely consistent with those of nab-paclitaxel monotherapy and were manageable in a similar fashion to weekly nab-paclitaxel. Across all dose levels and dosing regimens, dose-limiting toxicities (DLTs) as defined by Grade 3 or higher toxicities leading to greater than 1 week delay of nab-paclitaxel during the first cycle of treatment consisted of neutropenia, febrile neutropenia, rash, thrombocytopenia, hand/foot syndrome, peripheral neuropathy, colitis, diarrhea, and mucositis, with AEs of neutropenia constituting the majority of the DLTs. Due to the DLTs of neutropenia, primary prophylaxis with G-CSF was mandated and neutropenia was manageable with this implementation. For the continuous relacorilant schedule, the dose regimen selected for further clinical evaluation was relacorilant 100 mg and nab-paclitaxel 80 mg/m^2 (administered on Days 1, 8, and 15 of a 28-day cycle) with G-CSF. Of the

13 evaluable patients at this dose level, 4 patients experienced DLTs (neutropenia [2], colitis, and peripheral neuropathy). The feasibility of this dose regimen was further evaluated in patients with previously treated pancreatic adenocarcinoma and was determined to be suitable for evaluation in this patient population. The highest starting relacorilant dose level tested in Study CORT125134-550 with the continuous regimen was relacorilant 150 mg in combination with nab-paclitaxel 80 mg/m^2. The single patient enrolled to the pancreatic cohort at this dose level experienced a DLT of Grade 3 rash; 1 of the 3 patients enrolled to the advanced solid tumor cohort at this dose level experienced a DLT of Grade 3 febrile neutropenia that led to greater than 1 week interruption of study drugs. This dose level was closed to further enrollment as an alternative dosing strategy of upward titration from a starting daily dose of relacorilant 100 mg was considered to be more favorable than starting at the higher dose. The pharmacodynamic effect of a GR antagonist for a given dose or exposure varies among individuals. Similarly, glucocorticoid hormone response is known to vary among individuals as well as within the same individual and has presented a challenge to scientists and clinicians when using GR agonists. In order to optimize the dose for each individual in the presence of by-patient variability in PK and sensitivity to GR antagonism and to minimize the exposure of individuals to potentially suboptimal doses, intrapatient dose escalation of relacorilant was deemed to be the recommended approach for the continuous regimen in advanced solid tumors, and intrapatient upward dose titration is now being used as the relacorilant dosing regimen across therapeutic areas. Therefore, in the current study and in the ongoing CORT125134-552 Phase 2 study, patients will initiate relacorilant treatment at 100 mg daily and those who may benefit from a higher dose of relacorilant and have tolerated the regimen in Cycle 1 or 2 will be allowed to take a higher dose in the next cycle.

The American Society of Clinical Oncology (ASCO) (Smith et al. 2015) recommends primary prophylaxis with G-CSF starting with the first cycle of chemotherapy in patients who have 20% or higher risk for febrile neutropenia based on patient-, disease-, and treatment-related factors. Due to these risk factors, early cohorts in Study CORT125134-550 without primary prophylaxis with G-CSF experienced febrile neutropenia at rates above 20%. The target patient population for the current study would be at high risk for febrile neutropenia due to risk factors of age (i.e. majority are expected to 65 years or older), advanced disease, previous chemotherapy/radiotherapy (i.e. requirement to have received 2 or more prior chemotherapy regimens), poor performance status or nutritional status, and multiple comorbid conditions.

Taking into account early clinical experience with relacorilant in combination with nab-paclitaxel and target patient population risk factors, the Sponsor anticipates that the risk of febrile neutropenia is sufficiently high to warrant primary prophylaxis with G-CSF. Therefore, in the current study primary prophylaxis with G-CSF will be used to mitigate the risk of hematologic toxicities.

[redacted] In Study CORT125134-550, relacorilant in combination with nab-paclitaxel was evaluated in patients under fasting, ad-lib, and nonfasting conditions with the hard-shell capsules. In the current study, patients will be advised to take their dose of relacorilant with food to provide for uniform dosing.

1.5 Benefits and Risks

Relacorilant is an orally active, high-affinity, potent antagonist of GR with good selectivity for GR over other steroid receptors. High rates of GR expression have been shown in several solid tumor types including pancreatic adenocarcinoma, and nonclinical and clinical data indicate that GR antagonism may play a role in enhancing or restoring chemotherapy sensitivity in the treatment of patients with pancreatic adenocarcinoma. Early efficacy signals have been observed in the Phase 1/2 study in refractory patients with pancreatic cancer at doses and regimens proposed in this study (Munster et al. 2018).

The current safety profile for the use of relacorilant in combination with nab-paclitaxel is based on preliminary data from a Phase 1/2 Study (CORT125134-550) in patients with solid tumors (Section 1.2.2.2). For patients receiving combination of relacorilant with nab-paclitaxel, neutropenia has been the most common dose-limiting toxicity. The risk of neutropenia will be managed in this study with mandatory prophylactic growth factors, monitoring, and dose reduction. Mucositis and rash are commonly observed toxicities, and these can be managed with topical treatments, including triamcinolone.

Patients will be closely monitored during the study and standard safety tests will be performed at regular intervals. Samples will be collected to determine standard PK parameters for relacorilant and/or its metabolites (CORT125336, CORT125337, and CORT125295). Samples will also be collected to determine standard PK parameters for nab-paclitaxel.

Concurrent therapy with strong inhibitors of CYP3A4 or CYP3A5 should be avoided, particularly drugs with a narrow therapeutic ratio. Drugs with a narrow therapeutic ratio that are highly dependent on CYP3A4 for clearance should be avoided. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4, consistent with the nab-paclitaxel label.

See the relacorilant IB for further details on the benefits and risks.

2 STUDY OBJECTIVES

All study objectives apply to patients with mPDAC treated with relacorilant in combination with nab-paclitaxel.

2.1 Primary Objective

- To evaluate the ORR, defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR

2.2 Secondary Objectives

2.2.1 Efficacy Objectives

- To evaluate the ORR per RECIST v1.1, as assessed by the Investigator
- To evaluate best overall response per RECIST v1.1
- To evaluate the duration of response (DOR) according to the Investigator and BICR
- To evaluate DCR (CR, PR, or stable disease) at 18 weeks, as assessed by the Investigator
- To evaluate progression-free survival (PFS), as assessed by the Investigator
- To evaluate overall survival (OS)
- To evaluate PFS rate at 3, 6, and 12 months
- To evaluate OS rate at 3, 6, and 12 months
- To assess cancer antigen 19-9 (CA19-9) response at 8 and 16 weeks, in patients who have elevated CA19-9 at baseline
- To assess tumor response based on changes in fluorodeoxyglucose-positron emission tomography (FDG-PET) scan at 6 weeks per European Organization for Research and Treatment of Cancer (EORTC) criteria, according to BICR
- To evaluate the time to progression (TTP) on study treatment (relacorilant + nab-paclitaxel). The duration of disease control on prior nab-paclitaxel therapy (if applicable), and on the most recent therapy will also be described.

2.2.2 Safety Objectives

- To characterize the exposure-toxicity of relacorilant in combination with nab-paclitaxel
- To assess the safety and tolerability of relacorilant in combination with nab-paclitaxel

2.2.3 Pharmacokinetic Objectives

- To assess the PK of relacorilant in combination with nab-paclitaxel

2.3 Exploratory Objectives

- To assess the impact of relacorilant in combination with nab-paclitaxel on body composition, via computed tomography (CT)/magnetic resonance imaging (MRI) scans for sarcopenia
- To integrate changes in CA19-9 with tumor response rates by FDG-PET scan, in patients who have elevated CA19-9 at baseline
- To assess the changes in carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) at 8 and 16 weeks in patients who do not have elevated CA19-9 at baseline

- To assess changes in Karnofsky performance status (KPS) score

2.3.1 Pharmacodynamics/Biomarkers Objective

- To explore molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that have possible relevance to the mechanism of action of, or response/resistance to, relacorilant in combination with nab-paclitaxel

2.3.2 Patient-Reported Outcomes/Quality-of-Life Objective

- To assess PRO and QoL in terms of physical function, symptoms, and utilization of health care resources

3 STUDY DESIGN

3.1 Overall Design

This is a Phase 3, single-arm, open-label, multicenter study to assess the safety and effectiveness of relacorilant in combination with nab-paclitaxel in patients with mPDAC. Patients will enroll at approximately 30 centers in the US.

A detailed description of study visits and procedures is provided in Table 13.

The study consists of a single phase with the following study periods:

- **Screening Period:** Within 21 days prior to the first dose of relacorilant.
- **Treatment Period:** Both relacorilant and nab-paclitaxel will be administered during the Treatment Period, starting on Cycle 1 Day 1 and continuing until disease progression, unacceptable toxicity, or other treatment discontinuation criteria are met. Relacorilant (starting dose 100 mg) will be taken once daily and nab-paclitaxel 80 mg/m^2 will be administered on Days 1, 8, and 15 of each 28-day cycle. All patients, with exception of patients with absolute neutrophil count (ANC) >10,000/mm^3, will receive prophylactic G-CSF to reduce the risk of neutropenia starting 1 day after each nab-paclitaxel infusion. A minimum of 2 doses of G-CSF (filgrastim [5 µg/kg/day]) is recommended.
- **Safety Follow-Up Period:** Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of study treatment. Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments per the Schedule of Assessments (SoA) (every 6 to 8 weeks) until unequivocal disease progression.
- **Long-Term Survival Follow-Up Period:** All patients will be followed every 3 months after the end of treatment, to document dates and response to subsequent treatment, and for survival.

Patients with mPDAC who have received at least 2 prior lines of therapy for PDAC in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy will be eligible to enroll in the study.

Radiographic tumor assessments will be conducted using CT with contrast of the chest, abdomen, and pelvis using standard multiphasic (pancreas) CT imaging protocol guidelines. MRI of the chest, abdomen, and pelvis is acceptable, with Medical Monitor approval, if CT with contrast cannot be done. The same method should be used for each assessment for a particular patient. Prior to initiating therapy, a baseline tumor scan is required within 21 days prior to the first dose of relacorilant. Subsequent CT/MRI scans will be obtained every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days). CT/MRI scans will continue per this schedule until unequivocal disease progression is documented, including in patients who prematurely discontinue therapy. Tumor response will be assessed by BICR, and by the Investigator, using RECIST v1.1. CR and PR will be confirmed with a subsequent scan at least 4 weeks from the first response.

The same images (CT or MRI) acquired for radiographic tumor assessments will undergo additional imaging assessments for changes in skeletal muscle mass to determine the presence of sarcopenia.

A baseline FDG-PET scan will be obtained prior to initiating therapy and a post-baseline FDG-PET scan will be obtained 6 weeks (±7 days) from Cycle 1 Day 1.

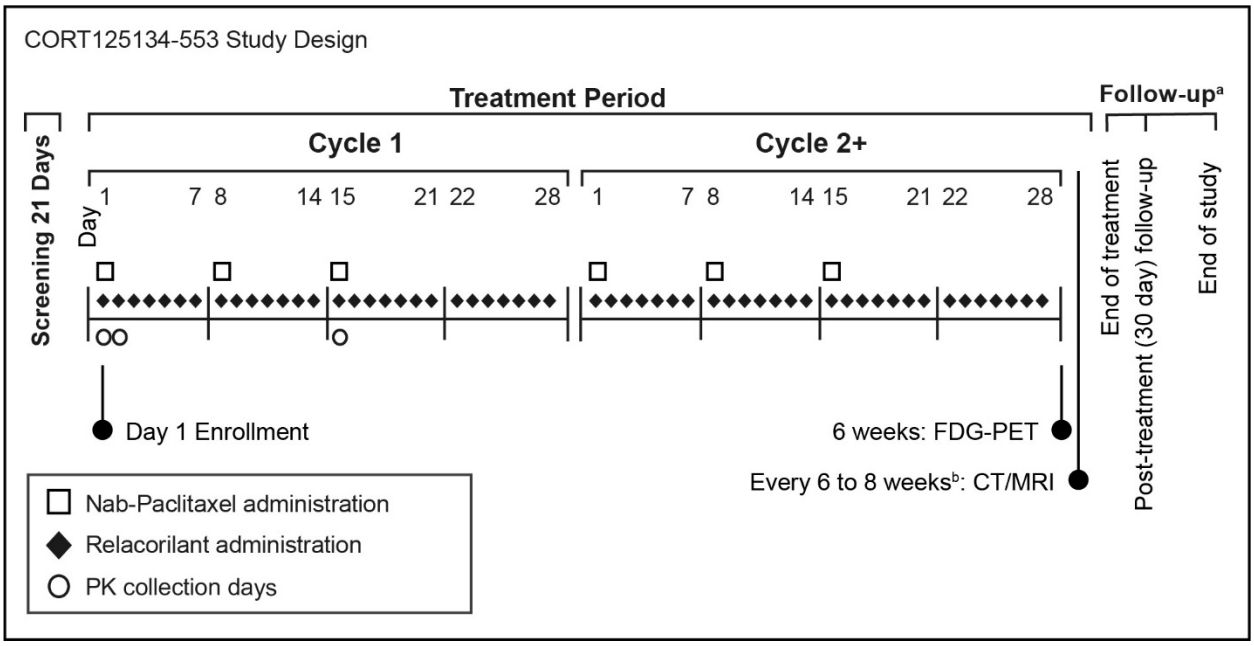
Radiographic scans will be quality checked, anonymized and stored centrally.

Patients will remain on treatment until unequivocal progressive disease (PD) per RECIST v1.1, as determined by the Investigator, or until meeting other criteria for discontinuation of the study regimen (Section 4.4.1). Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of relacorilant or nab-paclitaxel, whichever is latest, for a final visit (Section 7.5).

Patients will be followed for survival information (i.e., date and cause of death) and information on subsequent treatments (i.e., date/duration of treatment, response, and subsequent PD). Survival follow-up will continue every 3 months until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled (Section 7.6).

See Figure 2 for an illustration of the study design.

Figure 2 CORT125134-553 Study Design



CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; PK, pharmacokinetic.

[a] Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of study treatment. Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments (CT/MRI) every 6 to 8 weeks until unequivocal disease progression. Patients will continue to be followed for survival information every 3 months.

[b] Patients will have CT/MRI scans every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days).

Pharmacodynamics/Biomarkers

Patients will be requested to provide an archival or recent tumor biopsy, if available, for other exploratory markers relevant to pancreatic cancer or the mechanism of action. Patients will have the option to consent to provide an additional on-study biopsy obtained during a procedure conducted as part of their standard of care. Pharmacodynamic markers will include mRNA gene panel (blood and tumor expression profiles), cytokines, and other exploratory biomarkers.

Pharmacokinetics

PK will be characterized after dosing with the combination of nab-paclitaxel and relacorilant, on Cycle 1 Days 1, 2, and 15. Blood samples will be collected for determination of plasma PK parameters of relacorilant and/or its metabolites (CORT125336; CORT125337; CORT125295). Blood samples will be also be collected for determination of plasma PK parameters of nab-paclitaxel.

Patient-Reported Outcomes and Quality of Life

Baseline PRO and QoL assessments must be collected prior to the first dose of relacorilant. Post-baseline assessments will be collected at the beginning of every cycle starting with Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-day Post-Treatment Follow-Up Visit.

A detailed description of the study visits and procedures are provided in the SoA (Table 13), PK schedule (Table 14), and pharmacodynamic schedule (Table 15).

All data will be recorded in an electronic case report form (eCRF).

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR, defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR.

3.2.2 Secondary Endpoints

3.2.2.1 Secondary Efficacy Endpoints

Efficacy will be assessed by evaluating the following endpoints:

- ORR per RECIST v1.1, according to Investigator assessment
- Best overall response, defined as the best response recorded from the date of enrollment across all time points during study observation period, per RECIST v1.1 according to BICR
- Best overall response per RECIST v1.1 according to Investigator assessment
- DOR as measured from the date that the criteria are met for CR or PR until the first date that PD is objectively documented and determined by the Investigator
- DOR as measured from the date that the criteria are met for CR and PR until the first date that PD is objectively documented and determined by BICR
- DCR, defined as the percentage of patients who have achieved CR, PR, or stable disease for ≥18 weeks, as determined by the Investigator

- PFS, defined as the time from the date of enrollment to the date the patient experiences unequivocal disease progression per RECIST v1.1, as determined by the Investigator, or death (all causes of mortality)
- OS, defined as the time from date of enrollment until the date of death from any cause
- PFS rate (proportion of patients who have not progressed) at 3, 6, and 12 months
- OS rate (proportion of patients surviving) at 3, 6, and 12 months
- Change in CA19-9 from baseline at 8 weeks and 16 weeks in patients who have elevated CA19-9 (CA19-9 > upper limit of normal [ULN]) at baseline
- CA19-9 response, at 8 weeks and 16 weeks, defined as the percentage of patients with elevated CA19-9 at baseline who have ≥50% reduction in CA19-9
- Tumor response assessed by FDG-PET at 6 weeks per EORTC criteria, according to BICR
- TTP on study treatment, as determined by the Investigator

3.2.2.2 Safety Endpoints

Safety will be assessed by evaluating the following endpoints:

- Study drug exposure
- Exposure-toxicity and exposure-response of relacorilant and nab-paclitaxel
- AEs (including frequency, severity, and relationship to study treatment) and deaths
- Change from baseline in clinical laboratory tests
- Change from baseline in vital signs (including blood pressure, heart rate)
- Interpretation of electrocardiogram (ECG) assessments (normal, abnormal clinically insignificant, or abnormal clinically significant)
- Physical examination findings

3.2.2.3 Pharmacokinetic Endpoints

PK will be assessed by evaluating the following:

- Primary PK parameters of relacorilant and nab-paclitaxel estimated from PK sampling on Cycle 1 Days 1, 2, and 15

3.2.3 Exploratory Endpoints

3.2.3.1 Exploratory Efficacy Endpoints

- Presence of sarcopenia by CT/MRI scans of body composition (i.e., skeletal muscle mass)
- Change in CEA and CA-125 from baseline in patients who do not have elevated CA19-9 at baseline
- Change from baseline in KPS score

3.2.3.2 Pharmacodynamic Endpoints

Baseline assessment of:

- Homeostatic model assessment of insulin resistance (HOMA-IR)

- Immune and GC function-related cytokines
- Markers of sarcopenia or cachexia
- Hematology parameters, such as differential complete blood count
- RNA analyses from circulating cells and tumor tissue of immune, tumor, and GC-related genes such as cyclooxygenase 2 (COX2) and dual-specificity phosphatase 1 (DUSP1)
- Tumor somatic DNA mutation panel
- Tumor IHC: immune infiltrate, programmed death-ligand 1 (PD-L1), and other exploratory markers

Change from baseline of:

- HOMA-IR
- Immune and GC function-related cytokines
- Markers of sarcopenia or cachexia
- Hematology parameters, such as differential complete blood count
- RNA analyses from circulating cells of immune, tumor, and GC-related genes such as COX2 and DUSP1

3.2.3.3 Patient-Reported Outcomes and Quality-of-Life Endpoints

Changes from baseline of PRO and QoL scores according to the following instruments:

- National Comprehensive Cancer Network/FACT-hepatobiliary-pancreatic symptom index (NFHSI-18) (Butt et al. 2012)
- Patient-Reported Outcomes Measurement Information System (PROMIS) (Cella et al. 2007) short form
- EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L/VASc)
- A questionnaire for healthcare service utilization

3.3 Number of Patients and Study Participation

3.3.1 Number of Patients

Approximately 80 patients will be enrolled in the study.

3.3.2 Patient Study Completion

Patients are considered to have completed the study if they have completed all phases of the study including the Long-Term Follow-Up Assessments (Section 7.6).

3.4 Definitions: Enrollment, End of Treatment, End of Study, and Study Duration

3.4.1 Enrollment

Eligible patients will be considered enrolled once they have received the first dose of relacorilant on Cycle 1 Day 1.

3.4.2 End of Treatment

Refer to Section 4.4.1 for patients who discontinue treatment.

The end of treatment is defined as the date on which the patient received his or her last treatment, relacorilant or nab-paclitaxel, whichever is latest.

3.4.3 End of Study

Refer to Section 4.4.2 for patient withdrawal from the study.

The end of study is defined as the date of last contact (visit, telephone, email) with the last study patient. The Sponsor (Corcept) will ensure that the Institutional Review Board (IRB) and the regulatory authority are notified that the study has finished according to the Sponsor's standard operating procedures and/or local or national regulations.

3.4.4 Study Duration

The total patient accrual duration is expected to be 24 months, with an overall expected study duration of 42 months.

3.5 Study Termination by Sponsor

If the Sponsor, Investigator, Study Monitor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study site's participation should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Study termination and follow-up will be performed in compliance with applicable regulations.

3.6 Independent Data Monitoring Committee

An IDMC will be established to conduct periodic and ad hoc medical and/or statistical reviews of available data to protect the safety and ethical interest of patients and protect the scientific validity of the study. The IDMC will comprise independent consultants (medical and statistical) with relevant expertise, who will meet on a regular basis, and as needed for more urgent issues.

The IDMC will be provided with data from this study, including safety and efficacy variables, for periodic review. The first meeting of the IDMC will occur after 40 patients have enrolled and met the criteria for the interim assessment (Section 9.5.9), and will include review of efficacy and safety data. Enrollment will be paused such that the interim assessment can be conducted by the IDMC before additional patients are enrolled. Subsequent reviews of safety will occur as specified by the IDMC, with a minimum frequency of approximately 12 months. The IDMC may recommend changes in the protocol based on futility, toxicity, or compelling evidence of efficacy. Further details describing the IDMC composition, responsibilities, decision rules, and contents of data reports will be described in the IDMC Charter.

3.7 Imaging Assessments by Blinded Independent Central Review

BICR will be used to minimize bias in interpretation of the radiological findings and provide independent adjudication of assessments. Radiological findings will be reviewed by at least 2 central independent readers who are blinded to Investigator assessments and clinical data. In the event that there is a discordance between the 2 reviewers, a third radiologist will adjudicate the assessments of the first 2 radiologists and determine which of the 2 is the most accurate. Radiographic scans will be quality checked, anonymized and stored centrally. Further details will be provided in the imaging charter.

4 STUDY POPULATION

4.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

1. Have signed and dated IRB-approved informed consent form (ICF) prior to study-specific screening procedures. Note: Standard-of-care assessments completed before the ICF is signed can be used for eligibility if done within the 21-day Screening Period.
2. Are male or female patients ≥18 years old.
3. Have histologically confirmed PDAC with metastatic disease.
4. Have received at least 2 prior lines of therapy for PDAC in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy.
5. Have received no more than 4 prior lines of cytotoxic or myelosuppressive therapy for PDAC.
6. Have a measurable lesion at baseline (within 21 days prior to the first dose of relacorilant) per RECIST v1.1, as assessed by the Investigator.

   Note: Standard multiphasic (pancreas) protocols should be used for all radiographic tumor assessments. The exact same image acquisition and processing parameters should be used throughout the study.
7. Willingness to provide blood samples and tumor tissue (primary or metastatic) for research purposes.
8. Available assessments of CA19-9 (or CEA and CA-125 in non-CA19-9 elevated tumors) within 14 days prior to first dose of relacorilant.
9. KPS score of ≥70. Two observers are required to assess KPS. If discrepant, the one with the lowest assessment will be considered true.
10. Any significant or symptomatic amounts of ascites have been drained prior to enrollment.
11. Are able to take oral medications.
12. Have adequate gastrointestinal absorption. If the patient has undergone gastric bypass surgery and/or surgery of gastrointestinal or hepatobiliary tract, the patient must demonstrate adequate absorption as evidenced by albumin ≥3.0 g/dL, controlled pancreatic insufficiency (if present), and lack of evidence of malabsorption.
13. Have adequate organ and marrow function meeting the following criteria:
    a. ANC ≥1,500 cells/mm^3
    b. Platelet count ≥100,000/mm^3
    c. Hemoglobin ≥9 g/dL
    d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 × ULN (or ≤4 × ULN in patients with liver metastases)
    e. Total bilirubin ≤1.5 × ULN
    f. Creatinine clearance (measured or estimated) >45 mL/min/1.73m2
    g. Albumin ≥3g/dL (≥30 g/L)
14. Are not pregnant or lactating.
15. Patients of childbearing potential must use appropriate precautions to avoid pregnancy:
    a. Women who are postmenopausal or permanently sterilized are considered of nonchildbearing potential. A woman is postmenopausal if it has been ≥12 months since her last menstruation, without an alternative medical cause. Accepted methods

of permanent sterilization methods are hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy.

b. Women of childbearing potential must use a highly effective contraception with low user-dependency throughout the study and then for at least 6 months after the final dose of relacorilant or nab-paclitaxel, whichever is latest. Accepted methods of highly effective contraception with low user-dependency are:
    i. An intrauterine device (hormonal or nonhormonal), provided that the patient has tolerated its use for at least 3 months before enrollment and undertakes not to have it removed for 1 month after the final dose of study treatment.
    ii. Abstinence from heterosexual intercourse, when it is in line with the patient's preferred and usual lifestyle. Periodic abstinence and withdrawal are NOT acceptable.
    iii. Vasectomized partner provided that the partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success.
c. Oral hormonal contraceptives are NOT permitted.
d. Male patients should agree to use an adequate method of contraception starting with the first dose of study treatment through 3 months after the final dose of study treatment (relacorilant or nab-paclitaxel, whichever is latest). Male patients should not father a child while receiving study treatment (including refraining from sperm donation).

4.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Have pancreatic neuroendocrine tumors, lymphoma of the pancreas, acinar pancreatic cancer, or ampullary cancer.
2. Have known untreated parenchymal brain metastasis or have uncontrolled central nervous system metastases. Patients must not require steroids and must be neurologically stable without corticosteroids for a minimum of 3 weeks prior to Cycle 1 Day 1.
3. Have a clinically relevant toxicity from prior systemic cytotoxic therapies or radiotherapy that in the opinion of the Investigator has not resolved to Grade 1 or less prior to enrollment, including peripheral neuropathy that is ongoing and greater than Grade 1 in severity, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.
4. Have a history of hypersensitivity or severe reaction to either relacorilant or nab-paclitaxel, or to similar classes of either drug.
5. Have taken the following medications prior to enrollment:
    a. An investigational product, cytotoxic chemotherapy or targeted agent within 14 days.
    b. Radiotherapy within 21 days.
    c. Palliative radiotherapy within 1 week of Cycle 1 Day 1, or if toxicities from radiotherapy are Grade 2 severity or higher or have not recovered to baseline.
    d. Systemic or prescription strength topical corticosteroids for the purposes of treating a chronic nononcologic indication within 21 days.

6. Have a requirement for treatment with chronic or frequently used oral or inhaled corticosteroids for medical conditions or illnesses (e.g., rheumatoid arthritis, asthma, or immunosuppression after organ transplantation).
7. Are taking a concomitant medication that is a strong CYP3A or CYP2C8 inhibitor or inducer, or a substrate of CYP3A or CYP2C8 and has a narrow therapeutic window (See Appendix D).
8. Concurrent treatment with mifepristone or other GR antagonists.
9. Have any clinically significant uncontrolled condition(s) or any medical condition which in the opinion of the Investigator places the patient at an unacceptably high risk for toxicities or impair study participation or cooperation.
    a. History of significant cardiac disease defined as New York Heart Association class III or IV, myocardial infarction within 6 months of enrollment, or unstable angina within 6 months of enrollment.
    b. Active infection that requires parenteral antibiotics within 14 days.
    c. Bowel obstruction or gastric outlet obstruction within 14 days.
    d. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
    e. Advanced chronic obstructive pulmonary disease or hepatic cirrhosis.
10. Have had any major surgery within 21 days prior to enrollment.
11. Have had endoscopic retrograde cholangiopancreatography with persistence of any of the following:
    a. Bilirubin ≥1.5 × ULN
    b. Amylase >2 × ULN and abdominal pain or amylase >3 × ULN (with or without symptoms)
    c. Fever or signs of infection
    d. Decreasing hemoglobin or signs of blood loss
12. Have a history of human immunodeficiency virus (HIV) or current chronic/active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
    a. Patients with chronic or active hepatitis B as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction results may be performed and must be negative for enrollment.
13. Have a rapid decline in KPS score or serum albumin (≥20%), or have progressive pain symptoms indicative of rapid clinical deterioration, in the opinion of the Investigator, prior to enrollment. These patients will become ineligible if rapid decline is observed during the Screening Period.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not entered in the study. The reason for screen failure should be recorded.

A patient who has failed screening due to a reason that is temporary and expected to resolve (e.g., mild intercurrent infection) may be rescreened.

4.4 Patient Discontinuation of Treatment or Study Completion/Withdrawal

In this study, patient "discontinuation" refers to discontinuation of study treatment. Patients who discontinue study treatment will continue to be followed for the study endpoints. This may include patients who have discontinued treatment due to disease progression, toxicity, Investigator decision, or personal decision. These patients will continue with the End-of-Treatment and 30-Day Follow-up Visits, radiographic tumor assessments (if disease progression has not occurred), and survival assessments. If a patient wishes to discontinue treatment and refuses further study procedures, the patient should be asked if he/she is willing to continue with the survival assessments (which can be conducted over the telephone) (Section 7.6).

Patient study completion refers to completion of all study procedures and Long-Term Follow-Up Assessments (Section 3.3.2). Patient "withdrawal" refers permanent withdrawal and cessation of all study treatments, procedures, and assessments without further follow-up (withdrawal of consent). If a patient wishes to withdraw consent to further participation in the study entirely, including Long-Term Survival Follow-Up, this should be clearly documented (1) in the patient's medical record and signed by the Investigator and (2) in the clinical study database (i.e., eCRF).

4.4.1 Discontinuation of Study Treatment

Patients may discontinue treatment at any time at their own request, or they may have study treatment discontinued, at any time, at the discretion of the Investigator or Sponsor for safety or the inability of the patient to comply with the protocol-required SoA.

Reasons for study treatment discontinuation may include any of the following:

- Patient has PD per RECIST v1.1, as determined by the Investigator.
- Patient has unacceptable toxicity.
- Patient experiences an AE.
- Patient refuses further study treatment (follow-up permitted by the patient).
- The Investigator decides it is in the patient's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
  - The patient requires prohibited medications.
  - Clinically significant deterioration of the patient's medical status, as determined by the Investigator.
  - The patient requires alternative anticancer agents or radiation therapy.
  - The patient is not compliant with protocol requirements.
- Patient is pregnant.
- Any of the criteria listing in Section 4.4.2, as patients who withdraw/complete the study will also discontinue treatment.

Disease progression based on FDG-PET alone should not be used to make decisions regarding tumor response, patient management, or to discontinue treatment. A transient metabolic flare associated with changes in uptake and metabolism of [18F]-fluorodeoxyglucose (FDG) may occur early in treatment and should not be considered evidence of disease progression. Clinical deterioration or changes on FDG-PET that may be indicative of disease progression, including new "hot spots" suggestive of new lesions, should be confirmed by biopsy or CT/MRI scan per RECIST v1.1.

Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of study treatment, and should report any AEs, including SAEs, for 30 days after the last administration of study drug (see Section 8.1.2). Patients who discontinue study treatment prior to PD will continue radiographic tumor assessments per the SoA (every 6 to 8 weeks) until unequivocal disease progression. After patients experience PD, they will enter the Long-Term Survival Follow-Up Period, during which they will continue to be followed for survival information (see Section 7.6).

The date when the patient discontinues treatment and the reason for discontinuation must be recorded on the eCRF.

For guidelines about temporary interruption of treatment or treatment modifications, see Section 5.4.

4.4.2 Patient Withdrawal from Study/Study Completion

Patients may voluntarily withdraw from the study at any time.

Reasons for study exit may include the following medical or administrative reasons:

- Withdrawal of consent for further follow-up by the patient or legal representative
- Completed the study (Section 3.3.2)
- Death
- Termination of the study by the Sponsor
- Lost to follow-up

4.5 Replacement of Patients

Patients who withdraw from study early may be replaced, at the discretion of the Sponsor and the Investigator, to ensure that sufficient patients complete the study to achieve the objectives.

4.6 Restrictions During Study

The following restrictions apply to patients in this study (prohibited or limited-use medications are described in Section 5.5):

Dietary Restrictions—Foods such as grapefruit and Seville orange, including marmalade and juices made from these fruits will be prohibited from 14 days prior to the first dose of study treatment and until the last treatment cycle is completed.

Contraception—Women of childbearing potential and men who participate in this study must agree to use effective contraception as outlined in Section 4.1.

5 STUDY TREATMENTS AND MANAGEMENT

Study drug is defined as the investigational product, relacorilant. The co-administered drug in this study is nab-paclitaxel.

Study treatment consists of relacorilant and nab-paclitaxel administered to a study patient according to the study protocol.

5.1 Relacorilant

Relacorilant description, packaging, and store are described in Table 1. For further information, see the relacorilant IB.

Table 1 Relacorilant: Formulation, Administration, Packaging, and Storage

Specifications	Relacorilant
Description	For each capsule, relacorilant (CORT125134) is prepared [redacted]
Supplied	Study drug is supplied as softgel capsules, containing 100 mg (yellow capsule) or 25 mg (brown capsule) of relacorilant.
Unit dose strength(s)	100 mg, 25 mg
Dose level(s)	100 mg once daily, with titration up to 150 mg once daily, as tolerated (Section 5.1.1)
Administration	Orally, with 8 oz of room temperature water. Capsules are to be swallowed whole and should not be chewed, dissolved, or opened prior to swallowing.
Regimen	Administer relacorilant once daily in the morning, each day. Patients should be encouraged to take relacorilant with food except on days when protocol-specified assessments require fasting or if the patient is not able to tolerate food intake with the medication.
Restrictions	Medicines/foods known to strongly inhibit CYP3Aor CYP2C8, and substrates of CYP3A with a narrow therapeutic window should be avoided. See Section 5.5.
Missed doses	If noticed >6 hours after scheduled dose, skip dose and take next scheduled dose.
Dispensing study drug	Dispense to patients according to their visit schedule.
Packaging and labeling	Relacorilant softgel capsules, 25 mg or 100 mg, will be provided in bottles containing 30 capsules each. Each bottle will be labeled as required per country-specific requirements.
Storage	Store as follows: • In a secure location • At 20–25 °C (68–77 °F) • Excursions permitted 15–30 °C (59–86 °F) • Out of reach and sight of children

Note: Procedures for inventory, reconciliation, and destruction or return of study drug are provided in Section 11.6.

5.1.1 Relacorilant Dose Titration

Relacorilant dose will be increased in patients who tolerated the 100 mg once daily dose after the first cycle.

Cycle 2 Day 1

If during the first cycle of treatment, the patient did not experience any intolerable Grade 2 toxicities or Grade 3 or 4 toxicities attributed to study treatment, then the relacorilant dose will be escalated to 125 mg once daily, beginning on Cycle 2 Day 1.

Cycle 3 Day 1

For patients whose relacorilant dose has been escalated to 125 mg, if no intolerable Grade 2 nor any Grade 3 or 4 toxicities require dose reduction or omission of either relacorilant or nab-paclitaxel in Cycle 2, then the relacorilant dose can be escalated to 150 mg once daily, beginning on Cycle 3 Day 1.

If the dose was not escalated during Cycle 1 or 2, then the dose should not be escalated in future cycles. For all cycles, dose delays and reductions will be managed according to Section 5.4.1.

5.2 Nab-Paclitaxel

Details of the co-administered drug, nab-paclitaxel, are provided in Table 2.

Table 2 Nab-Paclitaxel: Formulation, Administration, Packaging, and Storage

Specifications	Nab-Paclitaxel (Abraxane)
Dosage formulation	The chemical name for paclitaxel is 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. The empirical formula is $C_{47}H_{51}NO_{14}$.
Supplied	Single-use 50-mL vial
Unit dose strength(s)	Each 50-mL vial contains 100 mg paclitaxel and approximately 900 mg of human albumin as a stabilizer.
Administration	Administer reconstituted formulation as an intravenous infusion over 30 minutes (±5 minutes).
Dose level(s)	80 mg/m^2
Regimen	Administer on Days 1, 8, and 15 of each 28-day cycle. Nab-paclitaxel infusions must be no less than 7 days apart.
Restrictions	On Cycle 1 Day 1 and Cycle 1 Day 15, the start of nab-paclitaxel infusion must be within 15 minutes after relacorilant dose.
Missed doses	Refer to Section 5.4.3 and Appendix C.
Dispensing study treatment	Nab-paclitaxel will be administered in the clinic.
Packaging and labeling	Refer to current prescribing information or Summary of Product Characteristics.

Specifications	Nab-Paclitaxel (Abraxane)
Storage	• Store un-reconstituted nab-paclitaxel should be stored at 20–25°C (68–77°F) in its carton. • Store vials should be stored in their original cartons. Use reconstituted paclitaxel immediately. If not used immediately, place the vial in its carton and store at 2–8°C (36–46°F) for a maximum of 8 hours. • Store both forms in an area free of environmental extremes and accessible only to study personnel. • Discard partially and completely used vials according to the site's guidelines Record disposition on the Study Drug Accountability Record Form.
Manufacturer	Commercially available (Abraxis Biosciences, LLC, a wholly owned subsidiary of Celgene Corporation)

5.3 Additional Treatments

All patients, with exception of patients with ANC >10,000/mm^3, will receive prophylactic G-CSF to reduce the risk of neutropenia starting 1 day after each nab-paclitaxel infusion. A minimum of 2 doses of G-CSF (filgrastim [5 µg/kg/day]) is recommended.

G-CSF should not be administered if ANC exceeds 10,000/mm^3. Pegfilgrastim may be used for patients with a chemotherapy-free window of 2 weeks.

Prophylactic treatment with G-CSF will be per protocol, as stated above. In addition, G-CSF treatment may be used to provide support for a patient with clinically meaningful neutropenia or to maintain dose intensity as consistent with the institutional guidelines and standard practice.

5.4 Dose-Adjustment Criteria

Every effort should be made to administer study treatment on the planned dose and schedule.

In the event of toxicity, dosing may be delayed, modified, temporarily interrupted, or permanently discontinued as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed.

If study treatment is interrupted for >28 days with the approval of the Medical Monitor, clinical laboratory assessments may also be interrupted, if clinically significant laboratory abnormalities have resolved to Grade 1 or baseline. Tumor assessments (CT/MRI and CA-125) and PRO/QoL assessments should continue per the SoA.

General chemotherapy dosing guidelines are provided in Appendix C.

Table 3 Dose Reductions or Delays Due to Adverse Events

Adverse Event	Nab-Paclitaxel Dose Modification	Relacorilant Dose Modification
Neutropenia: (ANC 1,000-1,499)	Day 1 of any cycle: • Delay Day 1 dose until ANC is 1,500 or higher Day 8 or 15 of any cycle: • No change	• Withhold dose until ANC is 1,500 or higher • Reinitiate at same dose level
Neutropenia: (ANC <1,000)	Day 1 of any cycle: • Delay Day 1 dose until ANC is 1,500 or higher. • Reduce 1 dose level Day 8 or 15 of any cycle: • Omit dose • Reduce 1 dose level	• Withhold dose until ANC is 1,500 or higher • Reinitiate at same dose level
Febrile neutropenia: Grade 3 or 4	• Withhold dose until fever resolves and ANC is 1,500 or higher. • Reduce 1 dose level	• Withhold dose until fever resolves and ANC is 1,500 or higher • Reinitiate at same dose level
Thrombocytopenia: (Platelets 50,000-99,999)	Day 1 of any cycle: • Delay Day 1 dose until platelet is 100,000 or higher Day 8 or 15 of any cycle: • No change	• No change
Thrombocytopenia: (Platelets <50,000)	Day 1 of any cycle: • Delay Day 1 dose until platelet is 100,000 or higher Day 8 or 15 of any cycle: • Omit dose and then reduce nab-paclitaxel by 1 dose level	• No change
Peripheral neuropathy: Grade 3 or 4	• Delay dose until symptoms improve to Grade 1 or better • Reduce 1 dose level	• No change
Cystoid macular edema	• Discontinue nab-paclitaxel	• Discontinue relacorilant
Cutaneous toxicity: Grade 3	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reinitiate at same dose level
Cutaneous toxicity: Grade 4	• Discontinue nab-paclitaxel	• Discontinue relacorilant

Adverse Event	Nab-Paclitaxel Dose Modification	Relacorilant Dose Modification
Mucositis: Grade 3 or 4	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reinitiate at same dose level
Diarrhea: Grade 3 or 4	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• Withhold dose until improvement to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reinitiate at same dose level
Other hematologic or non-hematologic AE: Grade 3 or 4	• Withhold dose until severity of AE improves to Grade 1 or lower, or to baseline if Grade 2 toxicity was present at study entry • Reduce 1 dose level	• For AEs attributable only to nab-paclitaxel, continue relacorilant unchanged. • For AEs attributable to relacorilant, withhold dose until severity of AE improves to Grade 1 or lower (or to baseline if Grade 2 toxicity was present at study entry) and reinitiate at the same or reduced dose level (see Section 5.4.1 for more details)

AE, adverse event; ANC, absolute neutrophil count.

5.4.1 Dose Reductions or Delays for Relacorilant

For any patient who experiences Grade 3 or 4 toxicity that is attributable to relacorilant but not nab-paclitaxel or the underlying disease, relacorilant will be interrupted until the toxicity resolves to ≤ Grade 1 or to baseline if Grade 2 toxicity was present at study entry. After recovery to ≤ Grade 1 toxicity, relacorilant will be resumed. If the patient is taking relacorilant 125 mg or 150 mg daily, then resume relacorilant at a lower dose (relacorilant dose reductions to occur in 25-mg increments) (Table 4). Daily relacorilant dose should not be lower than 100 mg. If dose reduction is required when the patient is taking relacorilant 100 mg daily, relacorilant will be discontinued and the patient will continue on nab-paclitaxel alone.

Table 4 Relacorilant Dose Level Summary

Relacorilant Dose Level	**Daily Dose**
Dose Level +2 (eligible patients to escalate on Cycle 3 Day 1) [a]	150 mg
Dose Level +1 (eligible patients to escalate on Cycle 2 Day 1) [a]	125 mg
Starting Dose Level	**100 mg**
Dose Level -1	Discontinue Relacorilant

[a] See Section 5.1.1 for details.

5.4.2 Management of Signs of Excessive Glucocorticoid Receptor Antagonism

For patients treated with relacorilant, signs or symptoms related to excessive GR antagonism may develop. If signs and/or symptoms of excessive GR antagonism such as malaise, fatigue, lethargy, weakness, anorexia, nausea, vomiting, abdominal pain, or altered mental status are present, particularly if coexistent, treatment with relacorilant should be interrupted and the Medical Monitor should be consulted to assist in evaluating whether treatment should continue. If excessive GR antagonism is suspected, standard supportive care (including fluid resuscitation as indicated) and medical therapy should be administered without delay. Systemic administration of corticosteroids should be considered (e.g., dexamethasone 4 mg daily for 3 days and then tapered by 1 mg per day, or as indicated based on clinical response). [redacted] In the event of significant trauma or surgery through 28 days after the final dose of relacorilant, supplemental glucocorticoids (GCs) and appropriate medical care may be needed to prevent excessive GR antagonism that may arise due to increased cortisol requirements in the perioperative period.

5.4.3 Dose Reductions or Delays for Nab-Paclitaxel

After Cycle 1 Day 1, if there is a delay in nab-paclitaxel administration for any reason, the following applies:

- If an infusion is delayed by >3 days, that dose may be skipped, and the patient may resume treatment with the next scheduled infusion if appropriate in the judgment of the Investigator.
- If treatment with nab-paclitaxel is delayed for >4 weeks (omission of nab-paclitaxel for >28 days), the Medical Monitor should be notified.

Nab-paclitaxel dose reductions should be made based on observed toxicities secondary to treatment (Table 3). Sequential dose reductions (Table 5) may be made at the discretion of the Investigator. A maximum of 2 dose reductions are allowed.

Table 5 Nab-Paclitaxel Dose Reductions

Nab-paclitaxel Dose Level	**Weekly Dose**
Starting Dose Level	**80 mg/m^2**
Dose Level -1	60 mg/m^2
Dose Level -2	60 mg/m^2 biweekly (on Days 1 and 15 of each cycle)

Note: Nab-paclitaxel administered on Days 1, 8, and 15 of each 28-day cycle unless otherwise noted.

5.5 Concomitant Medications and Procedures

5.5.1 Permitted Concomitant Medications

Best supportive care and treatment should be prescribed as appropriate to each patient to manage disease-related symptoms (e.g., anti-emetics, antibiotics, transfusions, nutritional support, and pain control) according to institutional guidelines or ASCO guidelines.

Permitted treatments also include standard therapies for concurrent medical conditions.

Patients must be instructed to notify the investigational site about any new medications they take after the start of study treatment. All medications (other than study treatments) administered within 30 days of study entry and during the study must be listed on the concomitant medications eCRF.

Concurrent anticancer therapy with agents other than relacorilant and nab-paclitaxel is not allowed. See Section 5.5.3 for other prohibited concomitant medications.

5.5.2 Permitted Concomitant Therapy Requiring Caution

Permitted medications to be used with caution from 1 week before first relacorilant dose through the 30-day Post-Treatment Follow-Up Visit are as follows:

- Warfarin: If used, conduct additional international normalized ratio (INR) monitoring.
- Sulfonylureas: If used, conduct close glucose monitoring to assess for diabetic control.
- Corticosteroids:
  - Systemic corticosteroids. Short courses of prednisone for non–cancer-related reasons are permitted if clinically required (e.g., as premedication for imaging contrast administration). Relacorilant treatment should be withheld during corticosteroid administration, and the Medical Monitor should be notified.
- Potent (Group 3) topical corticosteroids for treatment of oral mucositis is allowed. Use for other indications should be done with caution due to the potential for systemic absorption, and the Medical Monitor should be contacted to discuss the treatment approach.
- Marijuana is metabolized by the liver and interacts with CYPs, so should be used with caution with relacorilant.

Relacorilant is a strong inhibitor of CYP3A in vivo. In healthy subjects, the exposure area under the curve of midazolam was increased ~9-fold upon co-administration with relacorilant, relative to midazolam alone; therefore, due to the potential for drug-drug interactions, drugs with a narrow therapeutic ratio that are highly dependent on CYP3A for clearance should be avoided.

The metabolism of nab-paclitaxel is catalyzed, in part, by CYP2C8. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit CYP2C8 (Abraxane USPI 2018; Abraxane SPC 2019).

Due to potential drug-drug interactions, the following medications are permitted but must be used with caution or avoided, if possible, from 1 week before first relacorilant dose through the 30-day Post-Treatment Follow-Up Visit:

- Inhibitors of CYP2C8
- Sensitive substrates of CYP3A that do not have a narrow therapeutic index
- Moderate inhibitors of CYP3A
- Moderate inducers of CYP3A and CYP2C8

For examples of medications to be used with caution, see Appendix D.

5.5.3 Prohibited Medications

As the metabolism of both nab-paclitaxel and relacorilant are mediated in part by CYP3A, there is potential for CYP3A inhibitors to increase nab-paclitaxel and relacorilant exposure.

Medicines/food known to strongly inhibit CYP3A are prohibited (see Section 4.6 for dietary restrictions).

The following medications are prohibited during treatment with relacorilant in this study:

- St. John's wort
- Strong inhibitors or inducers of CYP3A
- Substrates of CYP3A with narrow therapeutic windows
- Other investigational and antineoplastic therapies
- Other GR antagonists (e.g., mifepristone)

Patients should be counseled to avoid consumption of grapefruit and Seville oranges (including marmalade and juices made from these fruits) from 14 days prior to the first dose of study treatment and until the last treatment cycle is completed.

Examples of medications that are prohibited or are to be used with caution are listed in Appendix D. It is not possible to produce an exhaustive list of medications that fall into the categories, so if in question, please refer to the appropriate product label. If the Investigator determines that such a medication is medically necessary, the Investigator will notify the Medical Monitor and discuss the Investigator's use of these medications and the Investigator's plans to medically monitor the patient.

5.5.4 Procedures

If a patient requires surgery during the study, then this needs to be discussed with the Medical Monitor. If surgery affects a target lesion, that patient will be considered nonevaluable for response from that point forward and will continue to be followed for disease progression.

Radiation therapy is not allowed during the study.

5.6 Method of Treatment Assignment and Randomization

This is a nonrandomized study (i.e., no randomization or allocation methods will be used in this study).

5.7 Blinding

This is an open-label study. No blinded study treatments will be used in this study. To reduce bias, the primary endpoint, ORR per RECIST v1.1, will be assessed based on BICR.

5.8 Dose Diary

Dose diary cards will be provided to patients, and patients will be instructed to return all unused relacorilant and the dose diary card at the study visits as indicated in the SoA (Table 13).

Patients should complete an entry in the dose diary card for each self-administered dose of relacorilant and note doses of any concomitant medications taken. Entries will include the

number of capsules as well as the date and time of relacorilant administration. On visit days, relacorilant should be taken in the clinic during the visit and after initial blood draws. Time and dose administered should be documented in the clinic charts.

5.9 Product Accountability and Treatment Compliance

Patients will be instructed to return all used and unused study drug containers at each study visit. Patient compliance with the dosing regimen will be assessed by reconciliation of the used and unused study drug. The quantity dispensed, returned, used, or lost must be recorded. Procedures for return and disposition of study drug by the clinical site are provided in Section 11.6.

6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in the SoA (Table 13).

Additional evaluations/testing may be performed at unscheduled time points, if deemed clinically indicated or necessary by the Investigator and/or the Sponsor, for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The Investigator and Sponsor will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the study schedule, is essential and required for study conduct, and the Investigator must ensure that trial procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the study schedule.

6.1 Informed Consent and Screening

Written informed consent must be obtained in order for a patient to participate in this study. The ICF, which has been approved by the appropriate IRB, must be signed by the patient before any study-mandated procedures are performed. Study patients must be notified of any changes that might affect their willingness to continue in the study in an update to the ICF and be given the opportunity to ask questions and/or withdraw consent. The patient's agreement must be documented in writing.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure (see Section 4.3), as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in Table 13.

6.2 Demographics and Baseline Disease Characteristics

Patient demographic data, including age, sex, and race will be documented at Screening.

6.3 Medical and Medication History

Medical history, including details regarding illnesses and allergies, date(s) of onset, and whether conditions are currently ongoing, and medication history will be collected on all patients during Screening. Any new or clinically significant changes in the patient's medical or oncologic history between providing informed consent and the first dose of study treatment will be recorded on the AE eCRF page.

The following information will be collected:

- Complete medical history, including documentation of any clinically significant medical condition.
  - Please note that if the patient has lost ≥15 lb (6.8 kg) over the 3 months prior to screening, "weight loss" should be entered as an active condition on the Medical History.
- History of tobacco and alcohol use.
- Presence and severity of any symptoms/conditions associated with pancreatic cancer including malabsorption or malnutrition.
- Detailed oncologic history, including but not limited to:
  - Date of primary cancer diagnosis
  - Anatomic site of primary tumor
  - Stage of primary tumor
  - Pathology (histology or cytology) of primary tumor
  - Surgical history, including previous Whipple procedure and residual disease at the completion of neoadjuvant treatment: complete resection (R0), residual tumor cells on resection margins (R1), or macroscopic residual tumor cells (R2)
  - Presence of biliary stent at screening
  - Anticancer and radiation treatments administered (including initiation and completion dates, type of modality, response, and reason for discontinuation)
  - Metastasis information (including the current sites of metastases, presence of liver or pulmonary metastases, presence of peritoneal carcinomatosis and histological markers)
  - Prior molecular testing/tumor profiling (including repeat biopsy from primary pathology, blood-based assays for molecular markers, and determinants of prognosis or drug sensitivity). The data collected will be the results of tumor molecular profiling or genetic testing relevant to the cancer. Where possible, a comprehensive report would be preferred to a summary or notes on the results.

6.4 Safety Measures

Safety will be determined from evaluation of AEs, physical examinations, clinical laboratory tests, vital signs, and ECGs at the times indicated in Table 13.

6.4.1 Physical Examinations

Physical examinations will be performed according to the SoA (Table 13).

A comprehensive physical examination will be performed at Screening, Cycle 1 (Days 1 and 15) and Day 1 of each subsequent cycle, at the End-of-Treatment Visit, and at the 30-day Post-Treatment Follow-Up Visit. A targeted physical examination will be performed at Days 8 and 15 of each cycle. Physical examination findings will be recorded in the appropriate eCRF by the Investigator or qualified designee.

6.4.2 Vital Signs

Vital signs will be measured at the visits indicated in Table 13 and will include resting heart rate, blood pressure, respiratory rate, and body temperature. Heart rate (beats per minute), systolic and diastolic blood pressure will be measured after patients have been at rest (seated) for at least 3 minutes. Blood pressure will be recorded in mm Hg. The heart rate should be recorded over 30 seconds or longer.

6.4.3 Height and Weight

Height and weight will be measured and body mass index calculated during Screening, and weight will be measured at each visit where a physical examination is performed (Table 13). Weight will be measured without overcoat and shoes, and with only light clothing.

6.4.4 Pregnancy Test (for Women of Childbearing Potential)

For female patients of childbearing potential, a quantitative serum or urine pregnancy test will be performed to confirm that the patient meets eligibility requirements. A serum or urine pregnancy test will be obtained within 48 hours prior to the first dose of relacorilant and reviewed prior to enrollment. Pregnancy tests will be repeated every 12 weeks (±7 days), or more frequently if required according to local requirements. Patients considered not of childbearing potential must be documented as being surgically sterile or postmenopausal (amenorrheic for ≥12 months).

If treatment with relacorilant is stopped for ≥7 days, a female patient of childbearing potential should have a negative pregnancy test before restarting study drug. If pregnancy test results are equivocal in patients with evidence to support lack of pregnancy, the results should be discussed with the Medical Monitor and the Investigator's interpretation with supporting information documented in the source documents.

6.4.5 Triplicate 12-Lead Electrocardiogram

Twelve-lead ECG tracings, in triplicate, will be obtained from all patients at the times indicated in Table 13. Patients should be lying down for at least 10 minutes before each ECG evaluation.

The Investigator or qualified designee will indicate on the site's copy whether the ECG was normal, abnormal but not clinically significant, or abnormal and clinically significant and document this on the ECG eCRF. Any new or worsened abnormality noted as clinically significant will be reported as an AE. The original ECG tracing or copy with the physician's assessment will be retained in the patient's records at the study site.

6.4.6 Adverse Events

Details on definitions and reporting of AEs are provided in Section 8.

All AEs will be recorded from the time of signing the ICF until 30 days after the final dose of study treatment. Patients should be monitored for AEs consistent with the current IB for relacorilant and the labeling for nab-paclitaxel.

6.4.7 Subsequent Anticancer Therapy Status and Survival Follow-Up

The Investigator or qualified designee will review and document all new anticancer therapy initiated after the final dose of study treatment. If a patient initiates a new anticancer therapy within 30 days after the final dose of study treatment, the Post-Treatment Follow-Up Visit must occur before the first dose of the new therapy.

Once new anticancer therapy has been initiated, the patient will move into the Long-Term Survival Follow-Up Period (Section 7.6).

6.4.8 Clinical Laboratory Assessments

6.4.8.1 Laboratory Parameters

Clinical laboratory tests to be performed are listed in Table 6 and should be performed according to the SoA provided in Table 13. Laboratory assessments for PK are described in Section 6.7. Samples for HOMA-IR assessment (insulin and glucose) are to be collected under fasting conditions at the time points specified in the pharmacodynamic schedule (Table 15) and the HOMA-IR calculated (Matthews et al. 1985).

Fasting status at the time of laboratory tests will be documented in the eCRF.

Samples will be processed at local and central laboratories as follows:

- Local laboratory: hematology, chemistry, glucose, insulin, coagulation (activated partial thromboplastin time [aPTT] and INR), urinalysis, and serum or urine pregnancy test, and tumor markers (CA19-9, CEA, and CA-125)
- Central laboratory: tumor characterization and mRNA expression tests (including COX2 and DUSP1 and GC-induced genes or biomarkers of GR activity), and PK assessments (see Section 6.7)

Local laboratory data will be used for immediate treatment decisions and for safety assessment. If laboratory tests for screening are performed greater than 2 days prior to the first dose of relacorilant, hematology and chemistry should be repeated with 48 hours of Cycle 1 Day 1 and reviewed prior to enrollment to confirm eligibility. After Cycle 1 Day 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to the study visit/nab-paclitaxel infusion.

The Investigator will review all local laboratory reports, evaluate the results, and sign/date the report. Laboratory values for an analyte that are outside of the normal range for that analyte per the applicable reference range will be identified and can be repeated at the Investigator's discretion.

Table 6 Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis (Dipstick)**
Red blood cell count Hemoglobin Hematocrit Platelet count White blood cell (WBC) count WBC with 5-part differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Sodium Potassium Calcium Chloride Phosphorus [a] Magnesium [a] Serum Creatinine Total bilirubin Albumin Alkaline phosphatase Lactate dehydrogenase (at Screening only) Aspartate aminotransferase Alanine aminotransferase Glucose, document whether fasting or nonfasting Blood urea nitrogen Uric acid Bicarbonate Total protein	Bacteria Blood Urobilinogen Nitrites Color Clarity pH Specific gravity Ketones Protein Glucose Bilirubin Leukocyte esterase
Coagulation	**Other [b]**	**Pregnancy Test**
International normalized ratio Activated partial thromboplastin time	HIV immunoassay [c] Hepatitis B/C serology [d]	Serum or urine β-HCG, if applicable
Tumor Markers	**Pharmacodynamic**	
CA19-9 CA-125 [e] CEA [e]	See Table 15 for details	

β-HCG, beta human chorionic gonadotropin; CA-125, cancer antigen 125; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.
Note: See Table 13 for the laboratory test schedule.
[a] Magnesium and phosphorus at Screening and Day 1 of each cycle only.
[b] Must be confirmed as negative prior to enrollment.
[c] Fourth generation immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen.
[d] Serologic assays for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), and anti-hepatitis C antibodies. In equivocal cases, PCR assay for hepatitis B or C may be performed and must be negative for enrollment.
[e] CA-125 and CEA will only be measured in those patients who do not have elevated CA19-9 at Screening.

6.4.8.2 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual. Long-term retention of biological samples is described in Section 11.5.

6.4.8.3 Blood Volume Summary

Blood samples will be used for analysis of safety laboratory, efficacy, PK, pharmacodynamic, and biomarker parameters (Table 6). The total volume of blood to be collected from each patient will be specified in the ICF.

6.5 Measures of Anticancer Activity

Tumors will be assessed using CT/MRI scans and response to treatment will be determined by using RECIST v1.1 (Eisenhauer et al. 2009; Appendix B). In addition, this study includes FDG-PET scans of tumors and measurements of circulating tumor markers (CA19-9 in patients with elevated CA19-9 at baseline; or CEA and CA-125 in patients without elevated CA19-9).

A baseline tumor scan with CT/MRI is required within 21 days prior to the first dose of relacorilant. CT scans/MRI scans with contrast of the chest, abdomen, and pelvis collected ≤21 days before the first dose of relacorilant do not have to be repeated for the baseline measurement, if they meet study quality criteria and are of the same methods and technique anticipated to be used for radiographic tumor assessments throughout the duration of the study. Patients must have measurable lesions at baseline per RECIST v1.1, as determined by the Investigator, to be eligible for the study. Imaging for other areas of suspected metastatic disease (e.g. neck, brain or bones) not covered by the required imaging should also be performed.

Subsequent post-treatment CT/MRI scans are required every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days). CT/MRI scans will continue per this schedule, irrespective of treatment delays, until unequivocal PD is documented, including in patients who discontinue treatment prematurely. To ensure comparability, the baseline tumor scans, and subsequent tumor scans to assess response should be performed using the same imaging technique, acquisition, and processing parameters in a patient throughout the study, unless medically contraindicated.

The use of CT from positron emission tomography (PET)/CT scans can only be used to assess tumor response per RECIST v1.1 if the CT scan is of diagnostic quality (i.e., use of intravenous contrast using a pancreas protocol).

Tumor response will be assessed by BICR, and by the Investigator, using RECIST v1.1. Treatment decisions will be based on the Investigator's assessment of disease, and not based on the assessment by BICR.

Confirmation of objective responses is defined as responses that persist on repeat imaging for 2 assessments with a time period of at least 4 weeks between the 2 assessments. The confirmatory scan should be obtained no earlier than 4 weeks from the initial determination of response, and within 5 weeks of response when feasible. At the Post-Treatment Visit, a CT/MRI scan will be performed if ≥4 weeks have elapsed since the last radiographic tumor assessment,

unless there is documented PD. If PD is documented, an additional radiographic tumor assessment is not required as part of the final visit.

A baseline FDG-PET scan will also be obtained prior to initiating therapy (collected ≤21 days before the first dose of relacorilant) and a post-baseline FDG-PET scan will be obtained 6 weeks (±7 days) from Cycle 1 Day 1. The area of coverage will be from the mid-thigh to the base of the skull, including additional areas of known or suspected disease. Accurate FDG injection and scan times, as well as weight height, and fasting time, must be recorded. For the FDG-PET review component of BICR, a single-reader paradigm will be used to review an individual patient's data sequentially by time point.

BICR readers will receive all radiographic images performed for tumor assessment from the sites. The process for image collection and transmission to the BICR readers are provided in the Site Imaging Manual.

6.6 Exploratory Efficacy Measures

6.6.1 Evaluation of Sarcopenia

The same images (CT or MRI) acquired for tumor assessments will undergo additional evaluation by BICR for changes in skeletal muscle mass to determine the presence of sarcopenia. The details for exploratory sarcopenia analysis will be documented in the imaging charter.

6.6.2 Circulating Tumor Markers

Circulating tumor markers (i.e., CA19-9 in patients with elevated CA19-9 at baseline, or CEA and CA-125 in those without elevated CA19-9) will be assessed every 4 weeks from Cycle 1 Day 1 for the first 12 months of treatment. Baseline and follow-up measurements for any given patient should be performed at the same laboratory using the same testing diagnostic method, when possible. Treatment decisions should not be made solely on the basis of changes in CA19-9. Increasing CA19-9 values potentially indicative of disease progression should be confirmed with an additional evaluation of CA19-9 and with radiographic tumor assessments per RECIST v1.1 to avoid discontinuing treatment prematurely.

6.6.3 Karnofsky Performance Status Score

See Table 7 for KPS score criteria; KPS score will be assessed by the Investigator or a qualified designee at the visits indicated in Table 13.

Patients must have a KPS score of ≥70 at Screening to be eligible for enrollment. Two observers are required to assess the KPS score at Screening. If the values obtained by each observer are discrepant, the one with the lowest assessment will be considered true.

For visits during the Treatment Period, KPS score will be assessed prior to the nab-paclitaxel infusion.

Table 7 Karnofsky Performance Status Score

KPS Score	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

KPS, Karnofsky performance status.
Source: Yates et al. 1980

6.7 Pharmacokinetic Assessments

Blood samples will be collected for determination of plasma concentrations of relacorilant and/or its metabolites (CORT125336, CORT125337, and CORT125295). Blood samples will be also be collected for determination of plasma concentrations of nab-paclitaxel (Table 14).

Standard PK parameters (Table 12) will be included in the characterization and evaluation of the dose-exposure relationship and related analyses. An assessment of the correlation of anticancer activity, AEs, and plasma drug concentrations of relacorilant and nab-paclitaxel will also be undertaken.

6.8 Pharmacodynamic/Biomarker Assessments

The development and improvement of therapies increasingly depends on insights gained from analysis of biomarkers. During this study and with the consent of patients (see Section 10.3.1), biological samples (e.g., blood, plasma, and serum) will be obtained, either for analysis during the study or future analysis. These samples will be used to develop a better understanding of the mechanisms of both treatment response (predictive biomarkers) and disease processes (prognostic biomarkers) and ultimately to identify which patients have a high probability to benefit from treatment with relacorilant and those who do not.

The tests will be conducted using a variety of techniques (e.g., IHC and DNA/RNA analysis). Pharmacodynamic assays may be performed to correlate results of biomarker assessments to the physiological effects of relacorilant. A schedule of pharmacodynamic assessments, with timing and frequency of sample collections is provided in Table 15.

6.8.1 Blood Collection for Glucocorticoid-Related Pathways and Exploratory Biomarkers

Blood will be collected by venipuncture. Samples are to be obtained at the time points indicated in Table 15. Pharmacodynamics will be assessed by measuring fasting blood levels of insulin and glucose. Immune biomarkers including cytokines and immune cell characteristics will also be assessed. Blood samples will also be tested for markers of sarcopenia/cachexia, such as C-reactive protein and interleukin 6.

An immune, tumor, and GC-related gene panel (including COX2 and DUSP1) will also be performed. In order to permit future bridging studies to other potential GC-related gene panel assays, 2 additional tubes of blood must be obtained from all patients to be tested at a future date. In the event of DNA/RNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

6.8.2 Tumor Biopsy Tissue Collection

Patients will be requested to provide an archival or recent tumor biopsy, if available. Patients will also have the option to consent to provide an additional on-study biopsy obtained during a procedure conducted as part of their standard of care.

Tumor biopsy samples will be evaluated for pharmacodynamic markers as indicated in Table 15.

6.9 Patient-Reported Outcomes and Quality of Life

PRO and QoL will be assessed in this study using the NFHSI-18 questionnaire (Butt et al. 2012), PROMIS (Cella et al. 2007) short form, EQ-5D-5L/VASc (Herdman et al. 2011), and a questionnaire for healthcare service utilization.

Baseline PRO and QoL assessments will be collected at Screening prior to the first dose of relacorilant. Post-baseline assessments will be collected every cycle starting with Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-Day Post-Treatment Follow-Up Visit. PRO assessments should be completed prior to discussing the results of tumor assessments with the patient.

Patients should be encouraged to respond to all of the questions. While the patient is still at the site, the Investigator or designee will need to check the forms for completeness. If a patient is not able to complete the forms for any reason, this should be documented in the source. If a patient is not able to come to the site, the questionnaire may be sent (e.g., mail, courier, email, electronically) with a request to complete the forms and return them to the site as instructed by the site staff.

6.10 Appropriateness of the Measures

Standard clinical, PK, statistical, and laboratory procedures will be utilized in this study. The efficacy measurements in this study are standard.

7 STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT

The SoA with scheduled visit dates and acceptable visit windows is provided in Table 13. A PK schedule is provided in Table 14. A pharmacodynamics schedule is provided in Table 15.

7.1 Screening (Within 21 days Before the First Dose of Relacorilant)

Screening will be within 21 days before the first dose of relacorilant and may take place on more than 1 day within the 3-week Screening Period. If a patient was screened more than 21 days before the date of their first administration of study drug, that patient must be rescreened. A patient who has failed screening due to a reason that is temporary and expected to resolve may be rescreened.

At the start of the Screening Period, the study will be discussed with the patient, and a patient wishing to participate must give written informed consent prior to any study-related procedures or change in treatment. The patient must also give written authorization regarding privacy requirements prior to any study-related procedures or change in treatment. After written informed consent is obtained, prospective patients will be evaluated for entry into the study according to the inclusion and exclusion criteria (Sections 4.1 and 4.2).

Available measurements of CA19-9 (or CEA and CA-125 in non-CA19-9 elevated tumors) are required within 14 days prior to first dose of relacorilant. Patients will be requested to provide an archival or recent tumor biopsy, if available, for exploratory markers relevant to pancreatic cancer or the mechanism of action.

A CT/MRI scan and FDG-PET scan of the chest, abdomen, and pelvis will be performed within 21 days prior to the first dose of relacorilant to evaluate disease status per RECIST v1.1.

The following Screening procedures will also be performed at the site:

- Record baseline demographics
- Record medical/oncologic history
- Record prior and concomitant medications
- Perform and review a serum or urine pregnancy test for female patients of childbearing potential prior to enrollment (48-hour window prior to the first dose of relacorilant)
- Assess KPS score
- Perform comprehensive physical examination
- Measure height
- Measure body weight
- Record vital signs
- Perform 12-lead ECGs (performed in triplicate)
- Collect laboratory samples: hematology, coagulation (aPTT and INR), serum chemistry, urinalysis, and hepatitis B and C serologies and HIV immunoassay
- Perform PRO/QoL assessments
- Record AEs (only if events that occur after the time written informed consent is obtained; see Section 8.1)

7.2 Cycle 1 Day 1

Patients should arrive at the clinic in the fasting state for this visit.

At the Cycle 1 Day 1 Visit, eligibility criteria will be confirmed to ensure patients continue to meet the inclusion and exclusion criteria. Eligible patients will then receive their first dose of relacorilant and be enrolled (Section 3.4.1) at this visit. Each patient enrolled will be assigned a patient number that will be used on patient documentation throughout the study.

Patients will undergo the procedures listed below and enter the Treatment Period:

- Perform and review a serum or urine pregnancy test for female patients of childbearing potential prior to the first dose of relacorilant (48-hour window from the first dose), if applicable
- Record concomitant medications
- Assess KPS score
- Measure weight
- Perform physical examination
- Provide dose diary card to all patients
- Dispense relacorilant (see Section 5.1)
- Administer nab-paclitaxel (see Section 5.2)
- Collect laboratory sample for serum chemistry and hematology
- Collect samples for measuring circulating tumor markers (CA19-9 in patients with elevated CA19-9 at baseline, or CEA and CA-125 in those without elevated CA19-9)
- Collect PK samples (see Table 14 for details)
- Collect samples for pharmacodynamic assessments (Table 15 for details)
- Record AEs (see Section 8.1)

7.3 Treatment Period

Visits will be conducted according to Table 13. The acceptable visit window for scheduling conflicts during the Treatment Period is +1 days for all visits, unless the window spans a weekend. Visit windows are relative to the most recent infusion of nab-paclitaxel (Appendix C). Refer to Section 5.4.3 for nab-paclitaxel infusion delays due to toxicity.

Study procedures at each visit will be performed according to the SoA (Table 13). Radiographic tumor assessments will continue every 6 to 8 weeks (±7 days) until unequivocal PD is documented in a patient.

Patients should come to the clinic in the fasting state for the following visits for pharmacodynamic assessments (Table 15): Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 15, Cycle 3 Day 1, Day 1 of every 3 cycles from Cycle 3, and at the End-of-Treatment Visit/upon disease progression.

The following procedures will be performed at all study visits during the Treatment Period according to Table 13:

- Record concomitant medications
- Assess treatment compliance. Patients will be instructed to return all unused study drug and their dose diary card at each visit.

The following procedures will be performed at all study visits except for Cycle 1 Day 2:

- Administer nab-paclitaxel according to schedule (see Section 5.2)
- Measure weight
- Perform physical examination
- Record vital signs
- Collect laboratory samples: hematology and serum chemistry

The following procedures will be performed on Day 1 of each cycle only, according to Table 13:

- Assess KPS score
- Provide new dose diary card to all patients
- Dispense relacorilant (see Section 5.1)
- Collect samples for measuring circulating tumor markers (CA19-9 in patients with elevated CA19-9 at baseline, or CEA and CA-125 in those without elevated CA19-9)
- Perform PRO/QoL assessments

7.4 End-of-Treatment Visit

Patients should come to the clinic in the fasting state for this visit for pharmacodynamic assessments.

The following assessments should be performed during the End-of-Treatment Visit according to the SoA (Table 13):

- Tumor assessments (CT/MRI) by RECIST v1.1
- Assess KPS score
- Record concomitant medications
- Perform physical examination
- Measure weight
- Record vital signs
- Perform 12-lead ECGs (performed in triplicate)
- Collect laboratory samples: hematology, serum chemistry, and urinalysis
- Collect samples for measuring circulating tumor markers (CA19-9 in patients with elevated CA19-9 at baseline, or CEA and CA-125 in those without elevated CA19-9)
- Assess treatment compliance. Patients will be instructed to return all unused study drug and their dose diary card at each visit
- Perform PRO/QoL assessments
- Collect samples for pharmacodynamic assessments (see Table 15 for details)
- Record AEs (see Section 8.1)

For patients who end study treatment but have not yet experienced PD, the radiographic tumor assessments will continue until unequivocal PD is documented.

7.5 30-day Post-Treatment Follow-Up Visit

The following assessments should be performed 30 days after the patient's final dose of study treatment (relacorilant or nab-paclitaxel, whichever is latest) according to the SoA (Table 13):

- Assess KPS score
- Record concomitant medications
- Perform physical examination
- Measure weight
- Record vital signs
- Collect laboratory samples: hematology, coagulation (aPTT and INR), serum chemistry, and urinalysis
- Assess treatment compliance. Patients will be instructed to return all unused study drug and their dose diary card.
- Perform PRO/QoL assessments
- Record AEs (see Section 8.1)

7.6 Long-Term Follow-Up Assessment of Survival

Patients who discontinue treatment at any time will continue to be followed for survival information (i.e., the date and cause of death, and subsequent treatments including date/duration of treatment, response, and PD on subsequent therapy). Survival information and post-therapy information will be collected at 3 month intervals (or as requested by the Sponsor to support data analysis) beginning on the date of progression and continuing until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled. Post-therapy information will include name(s) of post-therapy regimens, post-therapy dates of initiation and completion, and response to subsequent therapies and reason for discontinuation. Study staff will consult public records for survival status if patient withdraws consent.

7.7 Unscheduled Visits

As appropriate, assessments deemed clinically necessary by the Investigator may be done at unscheduled visits.

8 SAFETY EVENT DOCUMENTATION AND REPORTING

8.1 Adverse Event

8.1.1 Definition

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product that emerges or worsens relative to the patient's pretreatment baseline, whether or not it is considered to be related to the investigational product.

Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

8.1.2 Performing Adverse Events Assessments

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. The Investigator remains responsible for managing AEs that are serious or that cause a patient to withdraw before completing the study. Frequency of follow-up of any particular AE is left to the discretion of the Investigator. Duration of follow-up and requirements for immediate SAE reporting (within 24 hours of the event) are described below.

Safety results collected during the study (e.g., AEs, laboratory test results and physical findings) will be monitored on an ongoing basis by the Medical Monitor and Investigator.

Collection of AEs will start immediately following signing of the ICF and will continue until 30 days after the final dose of relacorilant or nab-paclitaxel, whichever is latest. Any worsening AEs or any SAEs that occur more than 30 days after the final dose of study treatment, which are attributed to study treatment, will also be recorded on the corresponding AE eCRF. Events of death that are considered related to study treatment, which occur more than 30 days after the final dose of study treatment, should also be recorded on the AE eCRF.

New signs or symptoms or worsening in severity of a cancer symptom that occur in association with PD should be recorded as AEs. AEs that occur after the first dose of study treatment and up to and including 30 days after administration of the final dose of study treatment will be considered TEAEs. AEs reported more than 30 days after the final dose of study treatment will be considered post-treatment AEs.

All AEs will be documented on the AE eCRF and in the patient's medical record. The following attributes must be assigned:

1. Description
2. Dates of onset and resolution
3. Severity (see Section 8.1.2.1)
4. Relationship to study treatment (see Section 8.1.4)

5. Seriousness criteria if applicable (see Section 8.2.2)
6. Action taken

The Investigator will actively solicit this information and assess the AEs in terms of severity and relationship to each study drug. AEs (including laboratory abnormalities that constitute AEs) should be described using a unifying diagnosis whenever possible, rather than individual underlying signs and symptoms. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. This treatment may extend beyond the duration of the study. The Investigator will record treatment and medications required for treatment of the AE on the appropriate pages of the eCRF.

If an AE leads to treatment discontinuation, the corresponding event must be recorded on the End-of-Treatment eCRF as the reason for treatment discontinuation. In the event that a patient is withdrawn from the study because of an AE, the corresponding event must be recorded on the End-of-Study eCRF as the reason for withdrawal.

All AEs considered to be related (see Section 8.1.4) to study treatment and all SAEs will be followed until resolved or until a stable status has been achieved (see Section 8.2 for details on SAE reporting).

All SAEs that are related to study treatment and unexpected (not reported in the reference safety information [RSI] in the IB or if the event is of greater severity or frequency than that described in the RSI) must be reported to the governing IRB as required by the IRB, local regulations, and the governing health authorities (see Section 8.2.2).

8.1.2.1 Adverse Event Follow-Up and Recording

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

8.1.3 Severity

The seriousness of an AE should not be confused with its severity. To describe the maximum severity of the AE on the AE eCRF, the Investigator will use the NCI-CTCAE, v5.0 (NCI 2017). For events not listed in the NCI-CTCAE, the definitions from the NCI-CTCAE provided in Table 8 should be used to evaluate the grade of severity for the AEs.

Table 8 Adverse Event Grades Based on the National Cancer Institute Common Terminology Criteria for Adverse Events

Grade	Description
1	**Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate:** minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, and managing money)
3	**Severe**: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	**Life-threatening:** Life-threatening consequences; urgent intervention indicated
5	**Death:** Death related to AE

Source: National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0 (NCI 2017)
AE, adverse event.

8.1.4 Relationship to Study Treatment

The Investigator responsible for the patient's care or qualified designee will assess causality of AEs and SAEs based on the causal attribution guidance in Table 9. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). Relationship to study treatment (relacorilant and/or nab-paclitaxel) will be assessed for all AEs.

Table 9 Causal Attribution Guidance for Adverse Events

Not related	An AE that is judged to be clearly due only to extraneous causes such as diseases, environment, and the like or for which it is temporally implausible to be related to use of the drug. The cause must be noted on the AE eCRF.
Possibly related	An AE that might be due to the use of the drug. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded. An alternative explanation is inconclusive, e.g., concomitant drug(s), concurrent disease(s).
Probably related	An AE that might be due to the use of the drug. The relationship in time is suggestive. An alternative explanation is less likely, e.g., concomitant drug(s) or concurrent disease(s).

AE, adverse event; eCRF, electronic case report form.

8.1.5 Expectedness

An AE, regardless of seriousness, is considered unexpected if not reported in the RSI in the IB or if the event is of greater severity or frequency than described in the RSI.

8.1.6 Clinical Significance

The Investigator is responsible for determining whether an AE is clinically significant for the patient or the study overall. Clinical significance will be documented in the patient's medical records with the AE information.

8.1.7 Clinical Laboratory Adverse Events

All out-of-range laboratory values will be determined to be clinically significant or not clinically significant by the Investigator. An abnormal laboratory value that leads to a dose modification/interruption, treatment discontinuation, or patient withdrawal from the study will be recorded as an AE on the eCRF. Other clinically significant laboratory values may be reported as AEs at the discretion of the Investigator.

8.2 Serious Adverse Events

8.2.1 Definition

An SAE is any AE that meets any of the following criteria:

- Results in death (i.e., the AE caused or led to the fatality).
- Is life-threatening (i.e., the AE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization (i.e., hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial reduction of the patient's ability to perform activities of daily living).
- Results in a congenital anomaly or birth defect (i.e., an adverse finding in a child or fetus of a patient exposed to study treatment before conception or during pregnancy).
- Involves other medically important conditions (i.e., the AE does not meet any of the above serious criteria but based on appropriate medical judgment, may jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria).

Important medical events that might not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.2 Reporting Serious Adverse Events

Any SAE occurring during the study period (beginning with informed consent) and for at least 30 days after the final dose of relacorilant must be reported within 24 hours to the designated safety contact (Section 8.2.2.1) and recorded on the SAE Form. All patients with an SAE must

be followed and the outcomes reported. The Investigator must supply the Sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

If an SAE results in death, the death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only one such event should be reported. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. The eCRF should reflect that the death was due to an AE with the corresponding reason (e.g., sepsis) documented.

If the primary cause of death is PD, the cause of death should be clearly identified on the Death eCRF as progression of the cancer under study.

All SAEs occurring from the time of informed consent until 30 days following the final dose of study treatment (relacorilant or nab-paclitaxel, whichever is latest) must be reported to the designated safety contact (Section 8.2.2.1) within 24 hours of the knowledge of the occurrence. After this period, Investigators should continue to report all deaths and SAEs that are considered to be related to prior treatment with study drug. Any death occurring greater than 30 days after the final dose of study treatment requires expedited reporting within 24 hours only if it is considered possibly or probably related to study treatment.

The Investigator or designee will complete the SAE reporting form, including whether the event was or was not related to the investigational drug and send to the designated safety contact. The clinical staff will obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient within the patient files.

The Investigator or designee will promptly inform the governing IRB of all serious, unexpected, drug-related events that occur at his or her site or per the IRB regulations. It is the responsibility of each site to submit Investigational New Drug (IND) Safety Reports, as applicable, provided to them by the Sponsor to their IRB as required by the IRB, local regulations, and the governing health authorities.

The Investigator or designee will fax or email additional follow-up information, if required and available, to the contact provided within 24 hours of receipt. This information should be included on a follow-up SAE Form, placed with the original SAE Form, and kept with the appropriate section of the eCRF and/or study patient file.

SAE reporting contact information is provided in Section 8.2.2.1.

8.2.2.1 Safety Reporting Contact

Covance Safety is the SAE reporting contact for this study and can be contacted via the following:

- Email: [redacted]
- Fax: [redacted]

8.2.2.2 Suspected Unexpected Serious Adverse Reactions

The Sponsor will ensure that the regulatory authority is informed promptly of any Suspected Unexpected Serious Adverse Reaction (SUSAR) for the investigational medicinal product in accordance with US Regulations and EU Directive 2001/20/EC. The reference document used for SUSAR reporting will be the RSI in the most current version of the IB for relacorilant and the current US package insert or Summary of Product Characteristics for nab-paclitaxel.

8.3 Pregnancy

8.3.1 Maternal Exposure

All pregnancies occurring during the study and within 30 days of the final dose of study treatment should be immediately reported to the Sponsor. The outcome of any conception occurring from the date of the first dose of study treatment through within 30 days of the final dose of study treatment will be followed and documented for up to 2 months after the completion of pregnancy.

8.3.2 Paternal Exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies should be followed and documented, if possible. To capture information about a pregnancy from the partner of a male patient, the Investigator or designee must first obtain the consent of the male patient's partner; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose of study treatment until 30 days after the final dose of study treatment should be followed and documented, for up to 2 months after the completion of pregnancy.

8.4 Treatment of Overdose

There is currently no experience with overdose of relacorilant. The Sponsor does not recommend specific treatment for an overdose; however, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until any symptoms resolve.
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.5 Emergency Sponsor Contact

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of the investigational product), study site personnel will apply appropriate medical intervention according to current standards of care and will contact the Medical Monitor.

9 STATISTICAL METHODS

9.1 Analysis Populations

The analysis populations are defined in Table 10.

Table 10 Definitions of Analysis Populations

Population	Description
ITT Population/Safety Analysis Population	All patients enrolled (see Section 3.4.1) and treated with at least 1 dose of study treatment
Evaluable Population	All patients in the ITT Population who have at least one post-baseline radiographic tumor assessment (with a result other than nonevaluable)
PK Population	All enrolled patients who have PK data collected and available for analysis

ITT, Intent-to-Treat; PK, pharmacokinetics.

9.2 General Statistical Considerations

The statistical analysis will be conducted by the Sponsor and/or its designee. Statistical methods will be prespecified and documented in detail in a statistical analysis plan (SAP), to be finalized before database lock.

All relevant data collected on the eCRF will be presented in by-patient data listings, to include the site identifier, patient number, and starting dose group. Listings presenting study data over time will include the dose of study drug the patient received at the time of data collection.

In general, continuous variables will be summarized by the number of patients with non-missing data, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of patients in each category. Time-to-event variables will be summarized using Kaplan-Meier estimates and plots.

Baseline will be defined as the most recent value prior to the first dose of relacorilant.

9.3 Hypothesis Testing

Analyses of safety and efficacy will focus on estimation of treatment effects via descriptive statistics and confidence intervals (CIs). No formal hypotheses testing is planned.

9.4 Sample Size Calculation

In this single-arm, estimation study, the efficacy analysis will include the calculation of a 95% CI around the ORR point estimate in the Intent-to-Treat (ITT) Population. The lower bound of the 95% CI for ORR will be evaluated to exclude 10%. This lower bound for the ORR is supported by historical data in studies of third-line therapies in the setting of mPDAC (Section 1.1). In addition to evaluating the point and interval estimate around the ORR, the efficacy in this study will be evaluated by examining the DOR, as well the DCR, of at least 18 weeks.

A total of 80 patients in the ITT Population are expected to provide sufficient precision for the interval estimates for ORR. In Table 11, the 95% CI estimates around ORR were obtained using

the Clopper-Pearson method (Clopper and Pearson 1934). Patients with no post-baseline radiographic tumor assessments available will be considered nonresponders.

Table 11 Two-Sided 95% Confidence Intervals of Objective Response Rates with 80 Patients in the Intent-to-Treat Population

Number of ORs	ORR Estimate	95% CI of ORR (%)
8	10.0%	4.4 – 18.8
10	12.5%	6.2 – 21.8
12	15.0%	8.0 – 24.7
14	17.5%	9.9 – 27.6
16	20.0%	11.9 – 30.4
18	22.5%	13.9 – 33.2
22	27.5%	18.1 – 38.6

CI, confidence interval; OR, objective response; ORR, objective response rate.

With 80 patients planned in the study, and assuming a median survival of 6.5 months, with 12 months of accrual, 18 months of study duration, and a 10% drop-out rate, approximately 50 OS events will be observed by the end of the study.

9.5 Analysis Plan

9.5.1 Patient Disposition

Patient disposition summaries will include the number of enrolled patients, the number of enrolled patients in each analysis population, the number of patients completing the study per protocol, and the number of patients terminating the study early by the primary reason for withdrawal.

9.5.2 Demographic and Baseline Data

Demographics baseline data will include frequency and percentages for categorical variables, and mean, SD, median, minimum, and maximum for continuous variables. Demographic and baseline characteristics will be summarized for all patients.

9.5.3 Prior and Concomitant Medications

Verbatim terms on eCRFs will be mapped to Anatomical/Therapeutic Chemical (ATC) class and Generic Drug Names using the most current version of the World Health Organization (WHO) Drug Dictionary at the time of the analysis. Concomitant medications will be summarized for all patients.

The duration of treatment on the prior nab-paclitaxel regimen (if applicable) and on the most recent treatment regimen will be calculated.

9.5.4 Efficacy Analyses

Response rate endpoints will be summarized by providing the point and interval estimates. Time-to-event variables will be summarized using Kaplan-Meier estimates and plots. Event probabilities at 4-, 6-, and 12-month time points and the median time-to-event (if estimable) will be presented.

9.5.4.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is defined in Section 3.2.1.

The primary analysis of ORR per BICR will be performed in the ITT Population. ORR will also be analyzed in the Evaluable Population, as a supportive analysis to the primary endpoint analysis. The point estimate and 95% CI will be provided using the Clopper-Pearson method (Clopper and Pearson 1934). Patients in the ITT Population with no valid post-baseline radiographic tumor assessments will be considered nonresponders.

9.5.4.2 Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined in Section 3.2.2.

Best overall response will be analyzed in the ITT and Evaluable Populations. It will be reported as the number and percentages of patients achieving CR, PR, stable disease, PD, and nonevaluable as their best response recorded from the date of enrollment across all time points during study observation period, according to BICR, and according to Investigator assessment. Patients who have a post-baseline scan that cannot be evaluated because of the quality of the image or other reasons will have "nonevaluable" recorded as their response at that visit. If all post-baseline scans are inevaluable, the patient will have "nonevaluable" recorded as their best response. Best overall response will be presented categorically and graphically as a waterfall plot.

DOR will be analyzed in the ITT and Evaluable Populations. DOR is measured from the date that the criteria are met for CR or PR until the first date that PD is objectively documented or death (all cause) whichever comes first. DOR will be analyzed using Kaplan-Meier methods. Censoring rules will be described in the SAP.

DCR will be analyzed in the ITT and Evaluable Populations. DCR is defined as the percentage of patients who have achieved confirmed CR or PR, or stable disease for ≥18 weeks. The point estimate and 95% CI will be calculated using the Clopper-Pearson method. Patients in the ITT Population with no valid post-baseline radiographic tumor assessment will be considered nonresponders.

PFS will be analyzed in the ITT and Evaluable Populations. PFS is defined as the time from enrollment to the date the patient experiences unequivocal disease progression per RECIST v1.1 or death (all causes of mortality), whichever comes first. PFS will be analyzed using Kaplan-Meier methods. Censoring rules will be described in the SAP.

OS will be analyzed in the ITT and Evaluable Populations. OS is defined as the time from enrollment until the date of death from any cause. OS will be analyzed using Kaplan-Meier methods. Censoring rules will be described in the SAP.

Estimates of PFS rates at 3, 6, and 12 months will be calculated using Kaplan-Meier methods.

OS rate (proportion of patients surviving) at 3, 6, and 12 months will be calculated using Kaplan-Meier methods.

Change in CA19-9 from baseline in patients who have elevated CA19-9 at baseline (baseline CA19-9 >ULN) will be reported for the ITT and Evaluable Populations. Summary statistics will be provided at each of the time points during the observation period.

Percentage of patients with elevated CA19-9 at baseline who have ≥50% reduction in CA19-9 at 8 and 16 weeks will be reported for the ITT and Evaluable Populations. The point estimate and the 95% CI (using the Clopper-Pearson method) will be reported.

FDG-PET tumor response will be summarized at 6 weeks for the ITT and Evaluable Populations. FDG-PET response will be reported as the number and percentages of patients achieving complete metabolic response, partial metabolic response, stable metabolic disease, and progressive metabolic disease according to BICR assessment of changes in standardized uptake values (SUVs) from the baseline FDG-PET scan to the post-baseline (6-week) scan using EORTC criteria (Young et al. 1999). The SUVs obtained from FDG-PET scans will be summarized by visit in a table and presented graphically in waterfall plots.

TTP on study treatment will be summarized in the ITT and Evaluable Populations. TTP is defined as the time from enrollment to disease progression per RECIST v1.1 as determined by the Investigator. TTP will be analyzed using Kaplan-Meier methods. Censoring rules will be described in the SAP.

9.5.4.3 Analysis of Exploratory Endpoints

The exploratory efficacy endpoints are defined in Section 3.2.3.

Presence of sarcopenia by CT/MRI scans of body composition (i.e., skeletal muscle mass) will be analyzed in the ITT and Evaluable Populations. The percent change in skeletal muscle mass from baseline will be summarized. Summary statistics will be provided at each of the post-baseline time points during the observation period.

Change in CEA and CA-125 from baseline, in patients who do not have elevated CA19-9 at baseline, will be reported for the ITT and Evaluable Populations. Summary statistics will be reported for each time point during the observation period.

The percentage of patients with elevated CEA who have ≥50% reduction in CEA, at 8 weeks and 16 weeks, will be reported for ITT and Evaluable Populations. Point estimates and 95% CIs (using Clopper-Pearson method) will be provided.

The percentage of patients with elevated CA-125 who have ≥50% reduction in CA-125, at 8 weeks and 16 weeks, will be reported for the ITT and Evaluable Populations. Point estimates and 95% CIs (using the Clopper-Pearson method) will be provided.

All PRO/QoL endpoints (Section 6.9) will be analyzed in the ITT Population and summarized for patients experiencing clinical benefit (response and/or disease control ≥18 weeks). Summary statistics will be provided for baseline and observed values at all post-baseline time points during

the observation period as well as changes from baseline. Details on analysis methods will be provided in the SAP.

9.5.4.3.1 Subgroup Analyses

The primary and secondary efficacy endpoints will be analyzed for the following subgroups of the ITT and Evaluable Populations:

- Prior progression on/after nab-paclitaxel-based therapy
- Prior lines of therapy (2 vs. ≥3)
- Demographics (age, gender, race)
- KPS score (≥70 to <90 vs. ≥90 to 100)
- Site of metastatic disease (lung and lymph nodes only vs. liver vs. other)
- Time since diagnosis of pancreatic ductal adenocarcinoma to time of informed consent
- Original tumor location (head vs. body vs. tail of pancreas)

9.5.5 Safety Analyses

Safety analyses will be conducted on the Safety Analysis Population as described in Section 9.1.

The incidence of TEAEs, defined as AEs occurring after the first dose of study treatment through 30 days after the final dose of study treatment, will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. TEAEs will be further summarized by severity and relationship to study treatment. For each patient, if multiple incidences of the same AEs occur, the maximum severity reported will be used in summaries.

All AEs (whether TEAEs or not) will be listed by individual patient, including information regarding onset, duration, severity, and relationship to study drug. SAEs and AEs that lead to withdrawal from the study will be listed by individual patient.

The following AEs will be summarized separately: AEs leading to discontinuation of study drug (relacorilant or nab-paclitaxel), dose reduction or interruption, Grade ≥3 AEs and SAEs.

All deaths and causes of deaths will be summarized and listed.

Clinical laboratory test results, vital sign measurements, and abnormal ECG values will be summarized by parameter, visit, and time point using descriptive statistics, to include the change from baseline values. Shift tables will be constructed that describe changes from baseline to the end of treatment.

By-patient safety listings will be provided.

9.5.6 Pharmacokinetic Analysis

PK parameters of nab-paclitaxel and relacorilant and its metabolites will be calculated, and analyte concentration versus time plots will be provided. Example PK variables for analysis are listed in Table 12; details of the PK analyses will be described in the SAP finalized before database lock. PK analyses will be performed on the PK Population (Section 9.1).

Table 12 Pharmacokinetic Variables for Analysis

$\%AUC_{ex}$	Proportion of $AUC_{0-\infty}$ estimated by extrapolation after t_z, as a percentage
λ_z	Apparent terminal rate constant
AUC	Area under the concentration-time curve
AUC_{0-24h}	AUC values from time 0 to 24 hours post-dose
$AUC_{0-\infty}$	AUC values from time 0 extrapolated to infinity
AUC_{inf}	AUC values from time 0 extrapolated to infinity
AUC_{last}	AUC values from time 0 to time of last measurable concentration
AUC_{0-tz}	AUC from time 0 until t_z
AUC_{tau}	AUC over a dose-interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration within a dose interval
CL/F	Apparent oral clearance
$t_{1/2}$	Apparent terminal elimination half-life
t_{lag}	Latest time after dosing before the first quantifiable concentration
T_{max}	Time to maximum concentration
T_{min}	Time of minimum concentration in a dose interval
t_z	Time after dosing of the last quantifiable concentration

9.5.7 Pharmacodynamic Analysis

Pharmacodynamic parameters and biomarker results will be listed and summarized using descriptive statistics, as appropriate. Biomarker and pharmacodynamic exploratory analyses will be further described in the SAP finalized before database lock. The GC-related gene panel will be assessed as defined in the SAP.

9.5.8 Patient-Reported Outcomes and Quality of Life

Data collected using the PRO instruments and QoL assessments will be listed and summarized using descriptive statistics.

9.5.9 Interim Analysis

The IDMC (Section 3.6) will perform an interim assessment of safety and efficacy (which will include all patients enrolled in the study) after 40 patients have enrolled and met at least one of the following criteria:

1) Completed at least 12 weeks of treatment, including the second radiographic tumor assessment and have at least 1 post-baseline tumor assessment with a result other than nonevaluable.

2) Discontinued the study due to disease progression or toxicity.

A total of 40 patients in the Evaluable Population are expected to provide sufficient precision for the interval estimates for ORR at the interim analysis in order to allow the IDMC to make an informed recommendation.

The following decision rules are proposed as guidelines for IDMC recommendations:

1) If the point estimate for ORR as assessed by Investigator is ≥20%, then continue with enrollment to a total sample size of 80 patients.
2) If the point estimate for ORR as assessed by Investigator is ≥10% and <20%, then the IDMC will consider the totality of the available evidence for efficacy and safety in making a recommendation to continue enrollment in this study. For this purpose, the IDMC will be provided with the summaries of the primary and key secondary endpoints, together with the summaries on safety endpoints.
3) If the point estimate for ORR is <10%, then no additional patients will be enrolled and the treatment with relacorilant 100 mg once daily and nab-paclitaxel 80 mg/m^2 will be considered futile.

Following this initial assessment of safety and efficacy, subsequent reviews of safety will be based upon the recommendations from the IDMC, with a minimum frequency of approximately every 12 months.

In reviewing interim trial results, the IDMC will consider the overall risk and benefit to study participants and will make recommendations regarding steps to ensure both patient safety and the continued ethical integrity of the study. The IDMC may recommend introducing changes in the protocol based on futility, toxicity, or compelling evidence of efficacy.

In making a recommendation to terminate the study for any reason, the IDMC will consider information on safety endpoints, as well as consistency of outcomes, secondary endpoints, and may consider additional evaluation of efficacy (e.g., calculated predictive probabilities). Further details on the interim analysis will be provided in the SAP and IDMC Charter.

10 ETHICAL AND LEGAL CONSIDERATIONS

10.1 Compliance with Investigational Review Board Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable local regulations. The protocol, ICFs, recruitment materials, and all patient materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled, and the Investigator must submit written approval to the Sponsor, before enrolling any patient. The Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB/IEC on receipt of amendments and annually, as local regulations require.

All changes to the consent form must be approved by the IRB; a determination will be made regarding whether previously consented patients need to be re-consented

The Sponsor is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the Investigator should be provided to the Sponsor or the Sponsor's designee.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

10.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and applicable regulatory requirements.

The Investigator will ensure that the study procedures outlined in this protocol will be conducted in accordance with applicable country and local regulations.

10.3 Protection of Human Patients

10.3.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative.

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

- The ICF will contain all of the elements required by ICH GCP and any additional elements required by local regulations.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for

future determination of active metabolite concentrations and possible biomarkers related to drug response.

- The patient's signed and dated ICF must be obtained before conducting any study procedures.
- The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, blood, plasma, serum and tissue samples may be retained for future analysis to help identify biomarkers of disease or relacorilant treatment.

10.3.2 Patient Confidentiality

To maintain patient privacy, all source documents, study reports, and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or their designee and regulatory authority access to the patient's original study records for verification of data gathered on source documents and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

10.3.3 Patient Privacy

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor or its designee, regulatory agencies, and the IRB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations from each patient or, if appropriate, the patient's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient, and the patient will be removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness, and assessing compliance with the protocol and adherence to regulatory and GCP requirements) will be performed by the Sponsor's Clinical Monitor or designee.

- Monitoring will be performed in accordance with applicable local and country regulations and guidance.
- Monitoring will include regular site visits and communication with the Investigator and site staff as appropriate to discuss and answer study questions; ensure compliance with the protocol; and ensure quality and integrity of the data.
- Monitors will ensure the site maintains an adequate supply of investigational products; any necessary supplies and ensure that appropriate storage conditions are maintained.
- Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; and ICH GCP.

Monitoring methods, responsibilities, and requirements will be outlined in a study monitoring plan.

11.2 Quality Management

As part of quality management based on a risk-based approach per ICH E6(R2):

> *Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.*
>
> *Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.*

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance audit during the study by the Sponsor or its designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

11.3 Documentation

11.3.1 Electronic Case Report Forms and Study Records

The Investigator must generate and maintain complete, adequate, accurate, reliable, and consistent records to enable full documentation of study conduct. Study data will be captured on eCRFs. Investigators must retain all original source documents, and the Sponsor or its designee will notify Investigators in writing when the trial-related records are no longer needed.

11.3.2 Access to Source Documentation

The Sponsor or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct.

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents (e.g., laboratory reports, x-rays, workbooks, and patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

11.3.3 Source Documents

Source documents are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, and ECGs. All data entered into the CRFs must be substantiated by a source document.

11.3.4 Study Files and Retention of Study Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor before disposing of any study records.

11.4 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual.

11.5 Long-Term Retention of Biological Samples

No samples will be retained long-term (i.e., beyond end of study and database closure) without prior written consent of the patient and IRB approval.

All long-term, retention samples will be retained by the Sponsor or its designee. The long-term retention samples will be coded to allow de-identification according to applicable regulatory guidelines.

If a study patient does not provide consent for the future use of the patient's samples, that patient's samples will be destroyed. After conclusion of this study, if a study patient provides consent, the long-term samples will be held for a period up to 10 years, after which they will be destroyed.

During the conduct of the study, an individual patient can choose to withdraw consent to have his or her samples stored for future research.

It is the responsibility of the trial site to ensure that samples are appropriately labeled in accordance with trial procedures to comply with all applicable laws.

11.6 Clinical Supplies

11.6.1 Inventory, Reconciliation, Return, and Disposition of Clinical Supplies

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures. Storage of study drug is described in Table 1.

11.6.2 Clinical Supply Inventory

A detailed inventory must be completed for all study drug. The study drug is to be used in accordance with the protocol by patients who are under the direct supervision of an Investigator. The study drug must be dispensed only by an appropriately qualified person to patients in the study.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug(s) received, patients to whom study drug is dispensed (patient dose specific accounting), and study drug lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on site clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.

11.6.3 Return or Disposal of Study Drug and/or Supplies

All clinical study drug and/or supplies will either be destroyed by the site per institutional policy, or be returned to the Sponsor or the Sponsor's designee for destruction.

Unused study drug may be destroyed on site, per the site's SOPs, but only after Sponsor has granted approval for drug destruction. The study monitor must account for all study drug in a formal reconciliation process, before study drug destruction. All study drug destroyed on site must be documented.

Documentation must be provided to the Sponsor and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by the Sponsor.

11.7 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of investigational product disposition is maintained. It is the responsibility of the Investigator to ensure that the investigational product is used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor or its designee and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the drug. At the end of the study, after final drug inventory reconciliation by the study monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to SOPs.

11.8 Post-Trial Care

There is no provision for continuation of the investigational drug beyond the end of study treatment. The Sponsor will work with the Investigator to ensure that study participants continue to receive appropriate care, which may include referral to an ongoing clinical trial, with this or another investigational treatment or may involve transition to medical management outside the research context.

11.9 Noncompliance with the Protocol

Prospective approval of deviations from the inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6.

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor in writing and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study patients. When a deviation from the protocol is deemed necessary for an individual patient, the Investigator must obtain approval in writing from the Sponsor.

Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the patient and/or the study.

Any significant protocol deviations affecting patient eligibility and/or safety must be reviewed and/or approved by the IRB and regulatory authorities, as applicable, prior to implementation.

11.10 Financial Disclosure

Investigators will be required to disclose any financial equity interests in the Sponsor and any conflicts of interest, as defined by the Sponsor.

11.11 Publication and Disclosure Policy

Corcept, as the Sponsor, has a proprietary interest in this study.

No individual publications will be allowed before publication of the multicenter results except as agreed with the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review before submission to the publisher.

The Sponsor will comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors requirements.

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APPENDIX A: SCHEDULES OF ASSESSMENTS

Table 13 Schedule of Clinical Assessments and Procedures

Study Period	Screening	Treatment Period							EOT Visit	30-day Post-Treatment Follow-Up [a]	Long-Term Follow-Up [b] (Every 3 months after EOT)
		Cycle 1				Cycle 2 +					
Clinic Visit (see Note below table for windows)	Within 21 days prior to the first dose of relacorilant	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15			
Informed Consent	X	X									
Review Inclusion and Exclusion Criteria	X										
Demographics	X										
Medical/Oncologic History	X										
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Serum/Urine Pregnancy Test [c]	X					X [c]					
Tumor Biopsy [d]	X										
Tumor and Sarcopenia (% Skeletal Muscle Mass) Assessment by CT or MRI [e]	X	Every 6 wks until 24 wks, then every 8 wks [e]							X		
FDG-PET scan	X					X [6 wks only]					
CA19-9, CA-125, and CEA [f]	X	X				X			X [f]		
Karnofsky Performance Status	X	X				X			X	X	
Physical Examination [g]	X	X		X	X	X	X	X	X	X	
Vital Signs	X	X		X	X	X	X	X	X	X	
Height	X										
Weight	X	X		X	X	X	X	X	X	X	
Hematology [h]	X	X		X	X	X	X	X	X	X	
Coagulation (aPTT and INR)	X									X	

Study Period	**Screening**	**Treatment Period**							**EOT Visit**	**30-day Post-Treatment Follow-Up [a]**	**Long-Term Follow-Up [b] (Every 3 months after EOT)**
		Cycle 1				**Cycle 2 +**					
Clinic Visit (see Note below table for windows)	Within 21 days prior to the first dose of relacorilant	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15			
Serum Chemistry [i]	X	X		X	X	X	X	X	X	X	
Urinalysis [j]	X								X	X	
Hepatitis B and C Serologies and HIV	X										
12-lead ECG (Triplicate)	X								X		
Provide Dose Diary Card		X				X					
Nab-paclitaxel Dosing (IV)		X		X	X	X	X	X			
Dispense Relacorilant		X				X					
Relacorilant Dosing (Once Daily, by Mouth)		◄						►			
Assess Treatment Compliance [k]			X	X	X	X	X	X	X		
PK Sampling [l]		X	X		X						
Pharmacodynamic Sampling [m]		X	X		X	X			X		
Patient-Reported Outcomes and Quality of Life [n]	X					X			X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Long-Term Follow-Up											X

aPTT, activated partial thromboplastin time; CA-125, cancer antigen 125; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ECG, electrocardiogram; EOT, End-of-Treatment; FDG-PET, fluorodeoxyglucose-positron emission tomography; GR, glucocorticoid receptor; HIV, human immunodeficiency virus; INR, international normalized ratio; IV, intravenously; PK, pharmacokinetics; wks, weeks.

Visit Window Note: Study visits will align with nab-paclitaxel infusion days during the Treatment Period. Refer to Appendix C for acceptable treatment windows for nab-paclitaxel based on scheduling, and Section 5.4.3 for dose delays due to toxicity.

Procedural Window Note: Screening hematology and chemistry laboratory tests can be used for Cycle 1 Day 1 values if collected within 48 hours of the first dose of relacorilant. For all other visits, pre-dose laboratory procedures can be conducted up to 72 hours prior to the study visit/nab-paclitaxel infusion. FDG-PET scan can be performed within a 7-day window.

[a] The Follow-Up Visit should be performed 30 days after the patient receives their final dose of study treatment (relacorilant or nab-paclitaxel, whichever is latest).

[b] Long-Term Follow-Up: survival information (i.e., the date and cause of death) and subsequent treatment information (i.e., date/duration of treatment, response, and disease progression on subsequent therapy). Follow-up will continue every 3 months until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled.

[c] A serum or urine pregnancy test for female patients of childbearing potential prior to the first dose of relacorilant (48-hour window from the first dose) and then every 12 weeks ±7 days.

[d] Patients will be requested to provide an archival or recent tumor biopsy, if available. Patients will also have the option to consent to provide an additional on-study biopsy obtained during a procedure conducted as part of their standard of care.

[e] CT/MRI scans will be performed within 21 days prior to the first dose of relacorilant and then every 6 to 8 weeks (±7 days) from Cycle 1 Day 1 (irrespective of treatment delays) until unequivocal disease progression is documented, including in patients who prematurely discontinue therapy. The same method should be used for each assessment for a particular patient. The same images (CT or MRI) acquired for tumor assessments will undergo additional evaluation for changes in skeletal muscle mass to determine the presence of sarcopenia. The details for analysis of sarcopenia will be documented in the imaging charter.

[f] Available measurements of CA19-9 (or CEA and CA-125 in non-CA19-9 elevated tumors) are required within 14 days prior to first dose of relacorilant. During the Treatment Period, circulating tumor markers (i.e., CA19-9 in patients with elevated CA19-9 at baseline, or CEA and CA-125 in those without elevated CA19-9) will be assessed every 4 weeks from Cycle 1 Day 1 for the first 12 months of treatment.

[g] A comprehensive physical examination will be performed at Screening, Cycle 1 Days 1 and 15, and Day 1 of each subsequent cycle, and at the End-of-Treatment Visit. A targeted physical examination will be performed at Days 8 and 15 of each cycle.

[h] Hematology assessments to include complete blood count with differential within 72 hours of study visit/nab-paclitaxel infusion.

[i] Serum chemistry assessments will include those listed in the clinical laboratory assessments table.

[j] Urinalysis at Screening, End-of-Treatment Visit, and 30-day Post-Treatment Follow-Up Visit. Microscopy is required only to follow-up clinically significant urine dipstick findings. Urinalysis assessments are listed in the clinical laboratory assessments table.

[k] Patient compliance will be assessed by reconciliation of the used and unused study drug.

[l] Pharmacokinetics will be characterized after dosing with the combination of nab-paclitaxel and relacorilant, on Cycle 1 Days 1, 2, and 15. Details are provided in Table 14.

[m] At Cycle 1 Day 1, samples will be collected pre-dose and at 4 hours post-dose. All other collections will be pre-dose. Details are provided in Table 15.

[n] Baseline patient-reported outcome assessments must be collected prior to the first dose of relacorilant. Post-baseline assessments will be collected every cycle starting with Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-day Post-Treatment Follow-Up Visit. Patient-reported outcome assessments should be completed prior to discussing the results of tumor assessments with the patient.

Table 14 Pharmacokinetic Schedule of Assessments

PK Sample	Day	Nominal Time	Window
Relacorilant and nab-paclitaxel	Cycle 1 Day 1 [a]	Pre-dose	<1 hour before relacorilant
		4 hours	From the start of nab-paclitaxel infusion ±10 minutes
	Cycle 1 Day 2 [a]	Pre-dose	<1 hour before relacorilant and within 30 minutes from the start of nab-paclitaxel infusion
	Cycle 1 Day 15	Pre-dose	<1 hour before relacorilant and within 30 minutes from the start of nab-paclitaxel infusion
		0.5 hour	From the start of nab-paclitaxel infusion ±10 minutes
		0.75 hour	
		1 hour	
		2 hours	
		4 hours	
		6 hours	

PK, pharmacokinetics.
[a] PK assessments on Cycle 1 Day 1 and Cycle 1 Day 2 are paired with identically scheduled biomarker assessments.

Table 15 Pharmacodynamic Schedule of Assessments

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
HOMA-IR	Blood	Fasting, pre-dose (preferably 7-9 am) at: Cycle 1 Day 1, plus an additional collection 4 hours post-dose Cycle 1 Day 2 Cycle 1 Day 15 Cycle 3 Day 1 Every 3 cycles from Cycle 3[a] EOT Disease progression [c]	*Fasting* blood glucose and insulin
Immune, tumor, and GC-related gene panel including COX2 and DUSP1	Blood	Fasting, pre-dose (preferably 7-9 am) at: Cycle 1 Day 1, plus an additional collection 4 hours post-dose Cycle 1 Day 2 Cycle 1 Day 15 Cycle 3 Day 1 Every 3 cycles from Cycle 3 [a] EOT Disease progression [c]	mRNA expression by technologies such as Nanostring
Exploratory cytokines, circulating tumor markers, and/or markers of sarcopenia or cachexia	Blood	Fasting, pre-dose (preferably 7-9 am) at: Cycle 1 Day 1, plus an additional collection 4 hours post-dose Cycle 1 Day 2 Cycle 1 Day 15 Cycle 3 Day 1 Every 3 cycles from Cycle 3 [a] EOT Disease progression [c]	Immunoassay panel for cytokines related to immune and GC function, markers of sarcopenia or cachexia (such as CRP and IL-6), and/or circulating tumor markers

Procedure/Assay	Tissue Source	Visit Schedule Cycle Day	Methodology; Examples of Biomarkers
Immune, tumor, and GC-related gene panel including COX2 and DUSP1	Tumor biopsy sample [b]	As provided (optional) [b]	Formalin fixed, paraffin embedded tissue sample; microdissection and assessment of mRNA expression of genes involved in tumor GR-signaling, chemotherapy resistance, tumor immune response, apoptosis, and metabolism
Immunohistochemistry for immune infiltrate, PD-L1, and other exploratory markers	Tumor biopsy sample [b]	As provided (optional) [b]	Formalin fixed, paraffin embedded tissue sample; assessment of immune infiltrate, PD-L1 IHC assay, and/or other histological methods
Mutation and homologous recombination deficiency assessment [d]	Tumor biopsy sample [b]	As provided (optional)	Formalin fixed, paraffin embedded tissue sample; DNA sequencing analysis, such as FoundationOne CDx™ panel

COX2, cyclooxygenase 2; CRP, C-reactive protein; DUSP1, dual-specificity phosphatase 1; EOT, End-of-Treatment; GC, glucocorticoid; HOMA-IR, homeostatic model assessment of insulin resistance; IHC, immunohistochemistry; IL-6, interleukin 6; PD-L1, programmed death-ligand 1.

[a] After 1 year, the sampling frequency will decrease to every 6 months.

[b] Patients will be requested to provide an archival or recent tumor biopsy, if available, for GR immunohistochemistry and other exploratory markers relevant to pancreatic cancer or the mechanism of action. Patients will also have the option to consent to provide an additional on-study biopsy obtained during a procedure conducted as part of their standard of care.

[c] If a patient discontinues treatment for reasons other than disease progression, a sample will be collected upon disease progression.

[d] If FoundationOne or comparable DNA mutation assay has been completed, de-identified data from biopsy is requested.

APPENDIX B: RESPONSE CRITERIA

Tumor response and assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 is described below. This appendix is not exhaustive and the source (Eisenhauer et al. 2009) should be referred to for further detail.

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Computed tomography (CT) is the best currently available and reproducible method to measure lesions selected for response assessment. CT (with intravenous and oral contrast) should be performed with cuts of 5 mm or less in slice thickness contiguously. Magnetic resonance imaging (MRI) can be performed if required but should have Sponsor approval.

For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions.

Measurable Tumors

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm on the long axis for non-nodal lesions by CT/MRI scan (slice thickness no greater than 5 mm).
- 15 mm on short axis for nodal disease by CT/MRI scan (slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).

Nonmeasurable Tumors

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal

masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Patients with measurable or nonmeasurable disease are eligible. Measurable disease is defined as above, by the presence of at least one measurable lesion.

Baseline Documentation of 'Target' and 'Nontarget' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to

reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Response criteria as defined below should be used:

- Evaluation of Target Lesions
  - Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
  - Partial Response (PR): At least a 30% decrease in the sum of the diameters (SOD) of target lesions, taking as reference the baseline SOD.
  - Progressive Disease (PD): At least a 20% increase in the SOD of target lesions, taking as reference the smallest sum recorded since the treatment started or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The development of unequivocal new lesions (not attributed to differences in scanning technique, imaging modality, or flare/healing of pre-existing lesions) will also be considered PD.
  - Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SOD since the treatment started.
- Special Notes on the Assessment of Target Lesions
  - Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, to qualify for CR, each node must achieve a short axis <10 mm. For PR, stable disease and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Evaluation of Nontarget Lesions
  - CR: Disappearance of all nontarget lesions and normalization of tumor marker level.
  - Incomplete Response/Stable Disease (non-CR/non-PD): Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
  - PD: Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.
- Special Notes on Assessment of Progression of Nontarget Disease
  - To achieve 'unequivocal progression' on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of stable disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- **A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal disease progression. In the absence of PD by CT/MRI per RECIST v1.1, an increase in uptake and metabolism of [^{18}F]-FDG is not sufficient to declare disease progression and should not be the basis for treatment discontinuation.** Clinical deterioration or changes on FDG-PET that may be indicative of disease progression, including new "hot spots" suggestive of new lesions, should be confirmed by biopsy or CT/MRI scan per RECIST v1.1.

APPENDIX C: GENERAL CHEMOTHERAPY GUIDELINES

- A patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol deviation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for nab-paclitaxel doses to be delivered within a 1-day window after the scheduled date of treatment, except if the treatment due date is a Friday. In that case, if the patient cannot be treated on the Friday, then the acceptable window for treatment would include the following Monday (Day 3 past due).
  For example:
  - "Day 8 chemotherapy" can be delivered on Day 8 or Day 9, unless Day 9 is a Saturday and then Day 8 chemotherapy can be delivered on Day 11
  - "Day 15 chemotherapy" can be given on Day 15 or Day 16, unless Day 16 is a Saturday and then Day 15 chemotherapy can be delivered on Day 18
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol deviation (most institutions use a rule of approximately ±5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes.
- If a patient has a dose interruption for >7 days, subsequent study visits/procedures may be omitted upon discussion with the Medical Monitor. Study assessments should be obtained and reviewed prior to the patient resuming study treatment. Radiographic tumor assessments should continue every 6 to 8 weeks, independent of treatment delays or interruptions, and AEs should be recorded during this time period according to Section 8.

APPENDIX D: EXAMPLES OF PROHIBITED MEDICATIONS OR MEDICATIONS TO BE USED WITH CAUTION

The following medications are examples (not a comprehensive list) of prohibited medications or medications to be used with caution or avoided, if possible, during the study:

	Prohibited	Permitted but Use with Caution or Avoid if Possible
CYP3A Inducers	St. John's wort, rifampin	Bosentan, efavirenz, etravirine, modafinil, nafcillin Carbamazepine, phenytoin
CYP3A Inhibitors	Grapefruit and Seville oranges (including marmalade and juices made from these fruits) Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil
CYP3A Substrates	Alfentanil, aprepitant, astemizole, budesonide, buspirone, cisapride, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, tolvaptan, tipranavir, triazolam, ticagrelor, vardenafil	--
CYP2C8 Inhibitors	Gemfibrozil	Glimepiride, tolbutamide [a]
Corticosteroids or GR Modulators	Mifepristone or other GR antagonists	Topical or oral corticosteroids

Abbreviations: CYP, cytochrome P450; GR, glucocorticoid receptor.

[a] For patients receiving sulfonylureas, conduct close glucose monitoring to assess for diabetic control.

Note: The table of examples above is not comprehensive. For additional information, see the prescribing information of the respective medications and the following websites for information on drug interactions: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm; http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX E: SUMMARY OF CHANGES

Significant changes in Amendment 1 dated 20 January 2020 of the protocol compared with the Original Protocol dated 08 July 2019 are summarized below with additional details provided in Table 16. Minor editorial or stylistic changes made for consistency are not shown in the redline version of the amendment.

This protocol amendment was written to:

- Change the study phase from Phase 2 to Phase 3 and adjust sample size estimates accordingly.
- Change inclusion criteria from "histologically confirmed mPDAC" to "histologically confirmed PDAC with metastatic" to clarify that histology from metastatic site is not necessary.
- Change in inclusion criteria so that prior lines of therapy could have occurred in any disease setting and are not restricted to the metastatic setting.
- Change timing of radiographic tumor assessments:
  - Post-baseline CT/MRI scans will now be conducted every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days).
  - A post-baseline FDG-PET scan will now be obtained 6 weeks (±7 days) from Cycle 1 Day 1.
- Add additional decision rules as proposed guidelines for IDMC recommendations at Interim Analysis.

Table 16 Summary of Changes in Protocol CORT125134-553 Amendment 1

Section	Revision
Global changes made but not shown in the redline version	Incorporated editorial and stylistic changes as appropriate (e.g., corrected typos, added hyphens, and defined acronyms). Updated the table of contents and the lists of tables and figures. Updated all table, figure, and section numbers.
Global changes made and shown in the redline version	For the version of the protocol, changed "Original" to "Amendment 1" and changed the date from 08 July 2019 to 20 January 2020. Updated study title to reflect the study name "RELIANT." Deleted text referring to Independent Ethics Committees (IECs) because this study will be conducted in the United States only. Updated citations and references, as appropriate. Updated study phase: Phase ~~2~~**3** Updated number of patients: ~~71~~**80** patients Updated periodicity of CT/MRI scans: every **6 to** 8 weeks Updated timing of post-baseline FDG-PET scan: **6**~~8~~ weeks (±7 days) from Cycle 1 Day 1 Added "radiographic" before tumor assessments, where appropriate, to clarify intent. Revised "last dose" to "final dose", where appropriate, to clarify intent. Revised text for consistency in using the term "the Sponsor" to indicate Corcept.
Cover Page	[redacted] and added [redacted] as Medical Monitor. Removed EudraCT number as the study will be conducted in the US only.
Synopsis	Updated the text in the synopsis to align with the changes in the following sections of the body of the protocol.
1 Introduction: Background Information and Scientific Rationale	Revised the last paragraph of this section: This Phase ~~2~~ **3** study **(RELacorilant In Pancreatic Adenocarcinoma with Nab-PacliTaxel [RELIANT])** is designed to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics, of relacorilant in combination with nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). Patients must have histologically confirmed ~~m~~**pancreatic ductal carcinoma (**PDAC**) with metastatic disease and have received at least 2 prior lines of therapy for pancreatic ductal adenocarcinoma (PDAC)**~~and documented disease progression on nab-paclitaxel~~ to participate.
1.1 Pancreatic Cancer	Revised the last sentence of this section to align with the updated statistical methodology: …the lower bound of the 95% CI for ORR will be evaluated to exclude ~~5~~**10**% (Section 9.4).
1.1.1 Therapeutic Hypothesis	Revised the text to align with the updated inclusion criteria.
1.2.1.2 In Vivo Studies	Replaced Figure 1 to remove "GR antagonist" from figure legend.
1.2.2 Clinical Summary	Updated the text related to safety and efficacy data in Study CORT125134-550 to align with the current version of the relacorilant Investigator's Brochure (Edition 7).
1.4 Rationale for Study Design and Dose Regiment	Revised text to align with updated inclusion criteria.
1.4.1 Differences Statement	Revised text to align with updated inclusion criteria.

Section	Revision
1.4.2 Rationale for Study Design	Revised text to align with updated inclusion criteria.
1.4.3 Rationale for Dose Selection	Added text to reflect current efficacy data from Study CORT125134-550: **Tumor response has also been observed in patients receiving relacorilant in combination with nab-paclitaxel in the Phase 1 Study CORT125134 550, including in patients who have previously received taxane treatment.**
1.4.4 Rationale for Dose Regimen	Modified text to reflect updated approach related to dosing: In the current study, relacorilant will be administered at 100 mg once daily (continuous dosing)**, with a possible increase to a maximum dose of 150 mg once daily (Section 5.1.1),** based on preliminary efficacy and safety results from Study CORT125134-550. ~~In this study, disease control of 16 weeks or greater has been observed in 7 patients with PDAC, including 4 patients with PDAC having PR on this combined treatment regimen (). Three of these patients achieved PR despite having progressed on 2 or more prior lines of therapy before entering the study (Section 1.2.2.1).~~ Added rationale for the dose regimen: **The initial starting dose of nab-paclitaxel in Study CORT125134-550 was 80 mg/m^2 when dosed with continuous relacorilant (100 mg) to account for the expected CYP3A-mediated drug-drug interaction resulting in increased nab-paclitaxel exposure. Overall, the toxicities observed with the dosing regimen were largely consistent with those of nab-paclitaxel monotherapy and were manageable in a similar fashion to weekly nab paclitaxel. Across all dose levels and dosing regimens, dose-limiting toxicities (DLTs) as defined by Grade 3 or higher toxicities leading to greater than 1 week delay of nab-paclitaxel during the first cycle of treatment consisted of neutropenia, febrile neutropenia, rash, thrombocytopenia, hand/foot syndrome, peripheral neuropathy, colitis, diarrhea, and mucositis, with AEs of neutropenia constituting the majority of the DLTs. Due to the DLTs of neutropenia, primary prophylaxis with G-CSF was mandated and neutropenia was manageable with this implementation. For the continuous relacorilant schedule, the dose regimen selected for further clinical evaluation was relacorilant 100 mg and nab-paclitaxel 80 mg/m2 (administered on Days 1, 8, and 15 of a 28-day cycle) with G-CSF. Of the 13 evaluable patients at this dose level, 4 patients experienced DLTs (neutropenia [2], colitis, and peripheral neuropathy). The feasibility of this dose regimen was further evaluated in patients with previously treated pancreatic adenocarcinoma and was determined to be suitable for evaluation in this patient population. The highest starting relacorilant dose level tested in Study CORT125134-550 with the continuous regimen was relacorilant 150 mg in combination with nab-paclitaxel 80 mg/m^2. The single patient enrolled to the pancreatic cohort at this dose level experienced a DLT of Grade 3 rash; 1 of the 3 patients enrolled to the advanced solid tumor cohort at this dose level experienced a DLT of Grade 3 febrile neutropenia that led to greater than 1 week interruption of study drugs. This dose level was closed to further enrollment as an alternative dosing strategy of upward titration from a starting daily dose of relacorilant 100 mg was considered to be more favorable than starting at the higher dose. The pharmacodynamic effect of a GR antagonist for a given dose or exposure varies among individuals. Similarly, glucocorticoid hormone response is known to vary among individuals as well as within the same individual and has presented a challenge to scientists and clinicians when using GR agonists. In order to optimize the dose for each individual in the presence of by-patient variability in PK and sensitivity to GR antagonism and to minimize the**

Section	Revision
1.4.4 Rationale for Dose Regimen (continued)	**exposure of individuals to potentially suboptimal doses, intrapatient dose escalation of relacorilant was deemed to be the recommended approach for the continuous regimen in advanced solid tumors, and intrapatient upward dose titration is now being used as the relacorilant dosing regimen across therapeutic areas. Therefore, in the current study and in the ongoing CORT125134-552 Phase 2 study, patients will initiate relacorilant treatment at 100 mg daily and those who may benefit from a higher dose of relacorilant and have tolerated the regimen in Cycle 1 or 2 will be allowed to take a higher dose in the next cycle.** **The American Society of Clinical Oncology (ASCO) (Smith et al. 2015) recommends primary prophylaxis with G-CSF starting with the first cycle of chemotherapy in patients who have 20% or higher risk for febrile neutropenia based on patient-, disease-, and treatment-related factors. Due to these risk factors, early cohorts in Study CORT125134-550 without primary prophylaxis with G-CSF experienced febrile neutropenia at rates above 20%. The target patient population for the current study would be at high risk for febrile neutropenia due to risk factors of age (i.e. majority are expected to 65 years or older), advanced disease, previous chemotherapy/radiotherapy (i.e. requirement to have received 2 or more prior chemotherapy regimens), poor performance status or nutritional status, and multiple comorbid conditions.** **Taking into account early clinical experience with relacorilant in combination with nab-paclitaxel and target patient population risk factors, the Sponsor anticipates that the risk of febrile neutropenia is sufficiently high to warrant primary prophylaxis with G-CSF. Therefore, in the current study primary prophylaxis with G-CSF will be used to mitigate the risk of hematologic toxicities.** [redacted] **In Study CORT125134-550, relacorilant in combination with nab-paclitaxel was evaluated in patients under fasting, ad-lib, and nonfasting conditions with the hard-shell capsules. In the current study, patients will be advised to take their dose of relacorilant with food to provide for uniform dosing.**
1.5 Benefits and Risks	Added text to reflect that PK parameters for relacorilant and its metabolites will be measured, as well as the standard PK parameters for nab-paclitaxel.
2.1 Primary Objective	Updated the wording: • To evaluate the ORR, defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR~~ of tumor scans~~.

Section	Revision
2.2.1 Efficacy Objectives	Modified the objectives to: • To evaluate the duration of response (DOR) according to the Investigator **and BICR** • To evaluate DCR (CR, PR, or stable disease) at ~~16~~**18** weeks, as assessed by the Investigator • To evaluate PFS rate at ~~2, 4,~~ **3**, 6, and 12 months • To evaluate OS rate at ~~4,~~ **3**, 6, and 12 months • To assess tumor response based on changes in fluorodeoxyglucose-positron emission tomography (FDG-PET) scan at ~~8~~ **6** weeks per European Organization for Research and Treatment of Cancer (EORTC) criteria, according to BICR • To evaluate the time to progression (TTP) on study treatment (relacorilant + nab-paclitaxel). The duration of disease control ~~and TTP~~ on prior nab-paclitaxel therapy **(if applicable)**, and on the most recent therapy will also be described.
2.3 Exploratory Objectives	Added an objective for KPS score, which is now an exploratory efficacy endpoint: • **To assess changes in Karnofsky performance status (KPS) score.** Revised the following exploratory objective to reflect the intent of capturing PRO and QoL endpoints: • To assess PRO **and QoL** in terms of physical function, symptoms, and utilization of health care resources.
3.1 Overall Design	Modified the text to reflect the increased number of study sites: Patients will enroll at approximately ~~25~~ **30** centers in the US ~~and globally~~. Modified text to reflect updated inclusion criteria: Patients with mPDAC who have received at least 2 prior lines of therapy **for PDAC in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy**~~and who had documented disease progression on nab-paclitaxel will be eligible to enroll in the study~~**.** Modified the text related to the timing of radiographic tumor assessments Subsequent CT/MRI scans will be obtained every ~~8~~ **6** weeks (±7 days) from Cycle 1 Day 1 **for 24 weeks**. **After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days). CT/MRI scans will continue per this schedule** until unequivocal disease progression is documented, including in patients who prematurely discontinue therapy. Replaced Figure 2 to reflect the updates to timing for CT/MRI and FDG-PET scans. Removed GR IHC under *Pharmacodynamics/Biomarkers*. Added the following text under *Pharmacokinetics*: **Blood samples will be collected for determination of plasma PK parameters of relacorilant and/or its metabolites (CORT125336; CORT125337; CORT125295). Blood samples will be also be collected for determination of plasma PK parameters of nab-paclitaxel.**
3.2.1 Primary Efficacy Endpoint	Updated the wording: The primary efficacy endpoint is ORR, defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR~~ of tumor scans~~.

Section	Revision
3.2.2.1 Secondary Efficacy Endpoints	Modified the text to add DOR per BICR as an efficacy endpoint and updated the endpoints to align with updated the timing of radiographic tumor assessments: • **DOR as measured from the data that the criteria are met for CR and PR until the first date that PD is objectively documented and determined by BICR** • DCR, defined as the percentage of patients who have achieved CR, PR, or stable disease for ≥~~16~~**18** weeks, as determined by the Investigator • PFS rate (proportion of patients who have not progressed) at ~~2, 4~~**3**, 6, and 12 months • OS rate (proportion of patients surviving) at ~~4~~**3**, 6, and 12 months • Tumor response assessed by FDG-PET at ~~8~~**6** weeks per EORTC criteria, according to BICR
3.2.2.2 Safety Endpoints	Removed the KPS score endpoint (now an exploratory efficacy endpoint): ~~• Change from baseline in Karnofsky performance status (KPS) score~~
3.2.3.1 Exploratory Efficacy Endpoints	Added an exploratory efficacy endpoint: • **Change from baseline in KPS score**
3.2.3.2 Pharmacodynamic Endpoints	Removed GR from the markers listed.
3.2.3.3 Patient-Reported Outcomes and Quality-of-Life Endpoints	Added EuroQoL 5 Dimensions 5 Levels to the endpoints, and formatted endpoints as bullets.
3.3.2 Patient Study Completion	Added definition of study completion.
3.4.2 End of Treatment	Revised text to clarify last treatment is relacorilant or nab-paclitaxel, whichever is latest.
3.6 Independent Data Monitoring Committee	Added the following statement: **Enrollment will be paused such that the interim assessment can be conducted by the IDMC before additional patients are enrolled.**
4.1 Inclusion Criteria	Revised the inclusion criteria: 3. Have histologically confirmed ~~m~~PDAC **with metastatic disease**. 4. Have received at least 2 prior lines of therapy for ~~m~~PDAC **in any setting,** ~~but no more than 4 prior lines of cytotoxic or myelosuppressive therapy for mPDAC. All adjuvant and neo-adjuvant therapies within the past 12 months will be counted toward the maximum lines of therapy~~ **including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy**. 5. Have received ~~at least 1 prior gemcitabine-based therapy and at least 1 prior fluorouracil-based therapy~~ no more than 4 prior lines of cytotoxic or myelosuppressive therapy for PDAC. ~~6. Have documented disease progression on nab-paclitaxel or within 90 days of the last dose of nab-paclitaxel therapy. Radiographic reports must be made available for documentation of disease progression.~~ ~~12. Have stable pain symptoms. Pain symptoms should not require modifications in analgesic management prior to enrollment.~~

Section	Revision
4.1 Inclusion Criteria	~~17.~~ **15.** Patients of childbearing potential must use appropriate precautions to avoid pregnancy: a. Women who are postmenopausal or permanently sterilized are considered of nonchildbearing potential. A woman is postmenopausal if it has been ≥12 months since her last menstruation, without an alternative medical cause. Accepted methods of permanent sterilization methods are hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy. b. Women of childbearing potential must use a highly effective contraception with low user-dependency throughout the study and then for at least 6 months **after the final dose of relacorilant or nab-paclitaxel, whichever is latest** ~~after the last dose of study treatment~~. Accepted methods of highly effective contraception with low user-dependency are:… c. Oral hormonal contraceptives are NOT permitted. d. Male patients should agree to use an adequate method of contraception starting with the first dose of study treatment through ~~120 days~~**3 months** after the ~~last~~ **final** dose of study treatment **(relacorilant or nab-paclitaxel, whichever is latest)**. **Male patients should not father a child while receiving study treatment (including refraining from sperm donation).**
4.2 Exclusion Criteria	Revised the exclusion criteria: 1. Have pancreatic neuroendocrine tumors, lymphoma of the pancreas, **acinar pancreatic cancer,** or ampullary cancer. 5. Have taken the following medications prior to enrollment: a. An investigational product, cytotoxic chemotherapy or targeted agent within ~~21~~ **14** days ~~or 5 half-lives, whichever is longer~~. b. Radiotherapy within 21 days. c. Palliative radiotherapy within ~~2~~ **1** weeks **of Cycle 1 Day 1, or if toxicities from radiotherapy are Grade 2 severity or higher or have not recovered to baseline.** ~~If palliative radiation therapy included the pelvis, a minimum of 3 weeks is required between palliative radiotherapy and enrollment.~~ d. Systemic~~, inhaled,~~ or prescription strength topical corticosteroids for the purposes of treating a chronic nononcologic indication within 21 days. 6. Have a requirement for treatment with chronic or frequently used oral **or inhaled** corticosteroids for medical conditions or illnesses (e.g., rheumatoid arthritis, **asthma, or** immunosuppression after organ transplantation). 7. Are taking a concomitant medication that is a strong ~~and moderate~~ CYP3A **or CYP2C8** inhibitor **or inducer**, ~~or a strong and moderate CYP3A inducer,~~ or ~~that is highly dependent on~~**a substrate** ~~metabolism by~~**of** CYP3A **or CYP2C8** and has a narrow therapeutic window (See Appendix D). **8. Concurrent treatment with mifepristone or other GR antagonists.** ~~8. Are women who are pregnant, lactating, or who intend to become pregnant within 3 months after the last dose of study treatment.~~ 11.Have had endoscopic retrograde cholangiopancreatography ~~within 7 days prior to enrollment~~**with persistence of any of the following:** **a. Bilirubin ≥1.5 × ULN** **b. Amylase >2 × ULN and abdominal pain or amylase >3 × ULN (with or without symptoms)** **c. Fever or signs of infection** **d. Decreasing hemoglobin or signs of blood loss**

Section	Revision
4.2 Exclusion Criteria (continued)	13. Have a rapid decline in KPS score or serum albumin (≥20%)**, or have progressive pain symptoms indicative of rapid clinical deterioration in the opinion of the Investigator,** prior to enrollment. These patients will become ineligible if rapid decline is observed during the Screening Period.
4.4 Patient Discontinuation **of Treatment** or **Study Completion**/Withdrawal	Wording in this section was revised to clearly indicate what should happen when a patient discontinues treatment, completes the study, or withdraws consent.
4.4.1 Discontinuation of Study Treatment	Reasons for treatment discontinuation were revised for clarity.
4.4.2 Patient Withdrawal from Study/**Study Completion**	Reasons a patient may exit from the study were revised for clarity.
~~4.4.3 Long-Term Survival Follow-Up~~	Removed this section as it is redundant with Section 7.6.
4.6 Restrictions During Study	Removed cranberry as a restricted food.
5.1 Relacorilant	Revised the text in Table 1 for consistency with the label provided on study drug. Added the recommendation to take relacorilant with food. Added information related to the permitted temperature excursions for study drug storage.
5.1.1 Relacorilant Dose Titration	Added text to reflect that the relacorilant dose can be increased to 150 mg, if tolerated.
5.2 Nab-Paclitaxel	Deleted text in row "Administration" which was redundant with the row "Regimen".
5.4 Dose-Adjustment Criteria	Revised the text in this section and added a table to specify the appropriate dose modifications for nab-paclitaxel and relacorilant, in case of toxicities.
5.4.1 Dose ~~Modifications~~ **Reductions** or Delays for Relacorilant	Revised the text and added a table of relacorilant dose levels (up to 150 mg and down to 100 mg) to provide guidance in case dose modification is needed.
5.4.2 Management of Signs of Excessive Glucocorticoid Receptor Antagonism	Modified the text to clarify that symptoms of GR antagonism could occur due to relacorilant treatment: ~~There is the possibility that~~**For** patients **treated with relacorilant,** could experience signs or symptoms related to excessive GR antagonism **may develop**.
5.4.3 Dose ~~Modifications~~ **Reductions** or Delays for Nab-Paclitaxel	Revised the text and added a table of nab-paclitaxel dose levels in case dose reductions are needed to provide clarification on what to do if the starting dose (80 mg/m^2) is not tolerated.
5.5 Concomitant Medications and Procedures	Revised the text to reflect: • Systemic corticosteroids are permitted if clinically required, for example as a premedication to a contrast agent • Marijuana is permitted but should be used with caution with relacorilant • Other GR antagonists are prohibited • Align text to the changes made to Appendix D (Examples of Prohibited Medications or Medications to be Used with Caution)
6.4.5 **Triplicate 12-Lead** Electrocardiogram	Revised the header and text to clarify that ECGs should be performed in triplicate.

Section	Revision
6.4.6 Karnofsky Performance Status Score	Moved to Section 6.6 Exploratory Efficacy Measures, as this is now an exploratory efficacy endpoint.
~~6.4.9~~ **6.4.8** Clinical Laboratory Assessments	Removed mean corpuscular volume, prothrombin time, and C-peptide and from the planned laboratory assessments. Modified the text in Table 6 for clarity: Serum or urine **β-HCG**~~pregnancy test~~
6.5 Measures of Anticancer Activity	Added text to clarify approach for areas of suspected metastatic disease: **Imaging for other areas of suspected metastatic disease (e.g. neck, brain or bones) not covered by the required imaging should also be performed.** Modified the text to reflect the updated periodicity of radiographic tumor assessments: Subsequent post-treatment CT/MRI scans are required every ~~8~~ **6** weeks (±7 days) from Cycle 1 Day 1 **for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days). CT/MRI scans will continue per this schedule,** irrespective of treatment delays, until unequivocal PD is documented, including in patients who discontinue treatment prematurely.
6.7.2 Evaluation of Sarcopenia	Moved to Section 6.6 Exploratory Efficacy Measures, as this is an exploratory efficacy endpoint.
~~6.7.1~~ **6.8.1** Blood Collection for Glucocorticoid-Related Pathways and Exploratory Biomarkers	Removed C-peptide from the list of assessments. Added the following text: **In order to permit future bridging studies to other potential GC-related gene panel assays, 2 additional tubes of blood must be obtained from all patients to be tested at a future date.**
6.9 Patient-Reported Outcomes and Quality of Life	Added EQ-5D-5L/VASc
7 Study Assessments and Procedures by Study Visit	Revised the text to align with the study schedule.
7.6 Long-Term Follow-Up Assessment of Survival	Revised text to provide details on the Long-Term Follow-Up Assessments.
8 Safety Event Documentation and Reporting	Revised text to clarify that clinically significant (rather than all) abnormal laboratory findings classify as AEs. Revised the text to specify that after the 30-day follow-up period AEs which worsen or SAEs, which are considered related to study treatment, should be recorded. Added text to indicate that any deaths considered related to study treatment occurring greater than 30 days after the final dose of study treatment should also be recorded. Removed Table 5 Follow-up Recording of AEs and Deaths as it was redundant with the text. Added text to section 8.1.4 and modified text in Table 9 to provide clarity on causality relationship. **Relationship to study treatment (relacorilant and/or nab-paclitaxel) will be assessed for all AEs.** Added the Safety Reporting Contact as Section 8.2.2.1.
9.1 Analysis Populations	Clarified the definition of the ITT Population.

Section	Revision
9.4 Sample Size Calculation	Revised the text to reflect the primary analysis will be in the ITT Population. Revised the text to align with the updated number of planned participants (changed from 71 to 80 patients) and timing of radiographic tumor assessments (changed from every 8 weeks to every 6 weeks). Revised the method for estimating CIs from Blaker to Clopper-Pearson method. Revised the expected number of OS events in Table 11 based on the updated statistical considerations.
9.5.3 Prior and Concomitant Medications	Revised text considering updated inclusion criteria (prior nab-paclitaxel therapy is no longer required).
9.5.4.1 Analysis of Primary Efficacy Endpoint	Revised the text to reflect the primary analysis will be in the ITT Population, with supportive analysis in the Evaluable Population.
9.5.4.1 Analysis of Secondary Efficacy Endpoints	Revised the text to reflect the data will be analyzed in the ITT and Evaluable Populations.
9.5.4.1 Analysis of Exploratory Endpoints	Revised the text to reflect the data will be analyzed in the ITT and Evaluable Populations. Replaced Blaker method with Clopper-Pearson method.
9.5.4.3.1 Subgroup Analyses	Added the following to the planned subgroup analyses: • **Prior progression on/after nab-paclitaxel-based therapy**
9.5.6 Pharmacokinetic Analysis	Revised the text to clearly indicate which analyses are planned. Removed $AUC_{glucose}$ from the table of PK parameters.
9.5.7 Pharmacodynamic Analysis	Revised the text to clearly indicate which analyses are planned.
9.5.8 Patient-Reported Outcomes and Quality of Life	Added a subsection to cover the analysis of PRO and QoL endpoints.
~~9.5.8~~ **9.5.9** Interim Analysis	Added decision rules for IDMC recommendations and reflected update to the sample size (from 71 to 80 patients) and efficacy endpoints.
11.2 Quality Management	Added a paragraph regarding a risk-based approach per ICH E6(R2), which is aligned with the current Corcept protocol template.
11.5 Long-Term Retention of Biological Samples	Revised the text to reflect the intended approach for the future use of patient samples.
12 References	Updated the references to match citations used in the text.
Appendix A	Revised Table 13 to align with updated the timing for radiographic tumor assessments, revisions to the clinical laboratory assessments, and for consistency with the changes in the protocol. Revised Table 15 to align with the changes in the protocol.
Appendix D	Updated Appendix D table to clarify which medications are prohibited or to be used with caution or avoid if possible, aligned with the prescribing information for nab-paclitaxel.

β-HCG, beta human chorionic gonadotropin; AE, adverse event; AUC, area under the curve; BICR, blinded independent central review; C_{max}, maximum concentration; CI, confidence interval; CR, complete response; CT, computed tomography; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; EORTC, European Organization for Research and Treatment of Cancer; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; FDA, Food and Drug Administration; FDG-PET, fluorodeoxyglucose-positron emission tomography; G-CSF, granulocyte colony-stimulating factor; ICH, International Council for Harmonisation; IDMC, Independent Data Monitoring Committee; ITT, Intent-to-Treat; KPS, Karnofsky performance status; mPDAC, metastatic pancreatic ductal adenocarcinoma; MRI, magnetic

resonance imaging; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic ductal carcinoma; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PRO, patient-reported outcomes; QoL, quality of life; SAE, serious AE; TTP, time to progression; ULN, upper limit of normal; US, United States.

Note: In this table, strike-through text indicates a deletion, bold text indicates an addition.